REVIEW Neuro/Head and Neck Radiology

Gadolinium deposition in the brain: current knowledge and recommendations

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ABSTRACT

Gadolinium based contrast agents (GBCAs) have been widely used intravenously in MRI examinations and are considered relatively safe in patients with intact renal function. However, since 2014, repeated administrations of GBCAs have been associated to high MRI signal intensity in deep brain nuclei, on unenhanced T1-weighted images, a finding that has been attributed to gadolinium (Gd) parenchymal deposition. Deep brain nuclei Gd deposition is variable among different agents available for clinical practice and is considered greater with linear GBCAs compared to macrocyclic agents. The clinical significance of Gd brain retention has not been extensively studied and remains, to a great extent, undetermined. In this review article, the biochemical structure of GBCAs, the clinical and pathologic studies investigating morphological and histological changes after multiple intravenous Gd administration, the suggested pathogenetic mechanisms and the recent recommendations towards safe use of these agents are summarised.

KEY WORDS: MRI; Gadolinium; Contrast agents; T1w sequences; Brain; Deposition

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Introduction

Gadolinium-based contrast agents (GBCAs) are commonly used intravenously in magnetic resonance imaging (MRI) examinations for the diagnosis and follow-up of various diseases [1]. They are known to act by shortening the T1 relaxation time of the abutting hydrogen nuclei, thus tissues with a high concentration of contrast exhibit enhanced tissue intensity in MR images. Since their introduction in 1987, over 300 million doses of GBCAs have been administered worldwide [2]. Rest aside minimal allergic reactions and adverse effects, GBCAs have long been considered relatively safe up until 2006, when Marckmann et al. reported that patients with severe renal impairment may develop nephrogenic systemic fibrosis (NSF) following GBCAs administration [3]. However, since renal function evaluation prior to GBCAs' administration, new NSF cases have been minimised [4].

In 2014 Kanda et al were the first to raise suspicion regarding central nervous system (CNS) accumulation of these agents. They reported high MRI signal intensity at the dentate nuclei (DN) and the globus pallidi (GP) on unenhanced T1-weighted (T1W) images, in adult patients, after repeated exposures to GBCAs [5]. Subsequently, numerous studies, in both adults and paediatric patients, further confirmed these findings and supported the theory of long-term CNS Gd retention after multiple GBCA-enhanced MRI scans [6-38]. In the same vein, there have been pathological human and animal studies that showed similar CNS Gd deposition patterns [39-51]. Therefore, concerns have been raised about safety and potential neurotoxicity, with ongoing controversy regarding the clinical impact of such a phaenomenon. In this review article we mainly focused on original articles published in peer-reviewed journals in the last five years aiming to summarise current knowledge and recommendations concerning Gd CNS deposition up to-date.

The biochemical structure of GBCAs

Gd in its free ionic form (Gd^{3+}) is a highly toxic lanthanide heavy metal. GBCAs represent a Gd ion bound to a chelating agent, which eliminates its toxicity and alters its distribution within the body [52]. GBCAs can be categorised into two broad groups based on their molecular structure: linear and macrocyclic. Macrocyclic -"caged"-ligands resemble a robust cavity enclosing the Gd ion, while linear-"open chain"-ligands wrap around the Gd ion, encircling it, without fully entrapping it. Each group can be further subclassified into ionic and non-ionic agents, according to their charge. The commercially available GBCAs comprise four different types: linear ionic, linear non-ionic, macrocyclic ionic, and macrocyclic non-ionic [53] (**Table 1**). According to their different chemical structures, these bear different properties regarding dechelation after administration. The linear non-ionic chelates are considered the least stable, whereas the macrocyclic ionic chelates are considered the most stable [54]. The higher the stability, the less likely that free Gd can be released into the circulation and tissues [55].

High signal intensity in deep brain nuclei on unenhanced T1W images is associated with previous GBCAs administrations (Fig. 1, Table 2)

Kanda et al were the first to report in 2014 that increased signal intensity in the DN and GP on unenhanced T1W images may be a consequence of multiple precedent linear GBCA administrations [5]. This study included 19 adult patients with brain tumours, having previously received at least six doses of linear GBCAs (gadopentetate dimeglumine or gadodiamide), and 16 patients having previously undergone at least six unenhanced MR examinations. The researchers calculated the mean signal intensity (SI) of the DN, GP, pons and thalamus on unenhanced T1W images and indicated that hyperintensity on T1W images in deep brain nuclei only developed in patients with exposure to GBCAs, with an increase in the dentate nucleus-to-pons and globus pallidus-to-thalamus SI ratios, that significantly correlated with the administered dose. No correlation with patients' renal function was demonstrated. Shortly after this initial report, these findings were confirmed in numerous studies and not only in patients with brain parenchymal diseases, such as multiple sclerosis (MS), gliomas and brain metastases, but, also, in patients with extraparenchymal lesions, such as meningiomas, who have a history of at least six MRI examinations with gadodiamide administration [9]. In these patient groups, a linear relationship was established between T1 hyperintensity of the DN and the number of enhanced MRI scans [6-18]. Even more, increased signal intensity on unenhanced T1W images was also seen in the posterior thalamus, substantia nigra, red nucleus, cerebellar peduncle, and colliculi in 13 patients who received 35 or more linear GBCA administrations [19], or even in the cortices of the pre- and post-central gyri and around

Table 1. Biochemical properties of gadolinium-based contrast agents.

Generic name	*Chemical structure*	*Ionic vs non-ionic*	*Trade name*
Gadopentetate dimeglumine	Linear	Ionic	Magnevist
Gadoversetamide	Linear	Non-Ionic	Optimark
Gadodiamide	Linear	Non-Ionic	Omniscan
Gadoteridol	Macrocyclic	Non-Ionic	Prohance
Gadoterate meglumine	Macrocyclic	Ionic	Dotarem
Gadobutrol	Macrocyclic	Non-ionic	Gadavist/Gadovist
Gadobenate dimeglumine	Linear	Ionic	Multihance
Gadoxetate disodium	Linear	Ionic	Primovist/Eovist

Table 2. Adult clinical studies investigating T1 hyperintensity of the brain structures after multiple GBCAs administration.

Adult Studies	*Patient groups*	*Contrast agent*	*MR System field Strength*	*Results*
Kanda et al., 2014 [5]	19 pts underwent more than 6 CE-MRIs; 16 pts underwent more than 6 unenhanced MRIs.	gadopentetate dimeglumine gadodiamide	1.5 T	High SI in DN and GP was associated with the number of previous CE-MRIs.
Errante et al., 2014 [6]	38 pts with MS underwent more than 2 CE-MRIs; 37 pts with brain metastases underwent more than 2 CE-MRIs.	gadodiamide	1.5 T	SI in DN has a linear relationship with the CE-MRI in pts with MS and brain metastases.
Radbruch et al., 2015 [7]	2 groups of 50 pts underwent at least 6 CE-MRIs.	gadopentetate dimeglumine gadoterate meglumine	1.5 T, 3.0 T	A SI increase in the DN and GP on T1-weighted images is caused by serial application of the linear GBCA gadopentetate dimeglumine, but not by the macrocyclic GBCA gadoterate meglumine.
Ramalho et al., 2015 [8]	18 pts with prior gadodiamide and current gadobenate dimeglumine administration; 44 pts with only gadobenate dimeglumine administration.	gadodiamide gadobenate dimeglumine	1.5 T	The gadodiamide exposed group showed greater T1 SI change compared to pts without prior gadodiamide exposures.
Quattrochi et al., 2015 [9]	46 pts with meningioma.	gadodiamide	N/A	Significant T1 hyperintensity of the DN on non-enhanced scans between the first and the last MRI in the group of patients with a history of at least 6 enhanced MRI scans.
Weberling et al., 2015 [10]	50 pts underwent more than 5 CE-MRIs.	gadobenate dimeglumine	1.5 T, 3.0 T	SI ratio in the DN was increased after repeated gadobenate imeglumine exposures.

Table 2. Adult clinical studies investigating T1 hyperintensity of the brain structures after multiple GBCAs administration.

Adult Studies	*Patient groups*	*Contrast agent*	*MR System field Strength*	*Results*
Adin et al., 2015 [11]	184 pts having received radiation therapy underwent 2677 MRIs.	gadopentetate dimeglumine	1.5 T, 3.0 T	Repeated CE-MRI administrations results in persistent increased SI in the DN on unenhanced T1WI.
Kanda et al., 2015 [12]	127 pts with various brain diseases.	23 pts linear chelate GBCAs, 36 pts macrocyclic chelate GBCAs 14 pts both types of GBCAs 54 pts no history of gadolinium chelate.	3.0 T	Hyperintensity in the DN on unenhanced T1-weighted MR images after administration of linear GBCA, and not with macrocyclic GBCAs.
Radbruch et al., 2015 [13]	50 pts with brain tumours and at least six consecutive MR imaging examinations with linear GBCAs and 50 pts with brain tumours and at least six examinations with macrocyclic GBCAs.	gadopentetate dimeglumine gadoterate meglumine	1.5 T, 3 T	SI increase in the DN and GP on T1-weighted images is caused by serial application of the linear GBCA gadopentetate dimeglumine, but not by the macrocyclic GBCA gadoterate meglumine.
Ramalho et al., 2016 [14]	62 pts with at least 3 gadobenate dimeglumine studies, (18 had previous administration of gadodiamide and 44 only gadobenate dimeglumine).	gadobenate dimeglumine gadodiamide	1.5 T	There is increased T1 signal change over time in patients who underwent gadobenate dimeglumine and had received prior gadodiamide, compared to those without exposure to previous gadodiamide.
Tedeschi et al., 2016 [15]	74 RRMS pts.	N/A	3 T, relaxometry (transverse R2* rate, longitudinal R1 relaxation rate)	The number of previous GBCA administrations correlates with R1 relaxation rates of DN, while R2* values remain unaffected, suggesting that T1-hyperintensity in these patients is related to the amount of Gadolinium given.
Radbruch et al., 2016 [16]	36 pts with at least 5 administrations of gadopentetate dimeglumine followed by 5 of gadobutrol.	gadopentetate dimeglumine gadobutrol	3 T	The application of the linear GBCA gadopentetate dimeglumine was associated with a DN-pons SI ratio increase, whereas subsequent applications of the macrocyclic GBCAs gadobutrol or gadoterate meglumine in the same patients were not.
Stojanov et al., 2016 [17]	58 RRMS pts divided in 3 groups based on the intervals of previous, multiple (n= 4-6) contrast administrations.	gadobutrol	1.5 T	T1-hyperintensity in both GP and DN in pts with RRMS after having received multiple gadobutrol exposures. Pts receiving doses with the shortest interval presented maximum increase in GP-to-thalamus SI ratio.

Table 2. Adult clinical studies investigating T1 hyperintensity of the brain structures after multiple GBCAs administration.

Adult Studies	*Patient groups*	*Contrast agent*	*MR System field Strength*	*Results*
Eisele et al., 2016 [26]	41 RRMS pts with at least 6 prior Gd-enhanced MRIs.	gadoterate meglumine	1.5 T, 3 T	No signal increases in the DN. No correlation between the mean DN-to-pons, or between the mean DN-to cerebellum SI ratio and the number of MRI examinations, disease duration and expanded disability status scale (EDSS).
Bjørnerud et al., 2017 [18]	17 pts with no previous history of linear GBCA administration.	gadobutrol	1.5 T	T1-hyperintensity of the DN, that correlated with the number of prior administrations.
Zhang et al., 2017 [19]	13 pts with more than 39 GBCAs exposures.	gadodiamide gadopentetate dimeglumine gadobenate dimeglumine	1.5 T, 3.0 T	Increased SI on unenhanced T1WI in the posterior thalamus, substantia nigra, red nucleus, cerebellar peduncle, colliculi, DN and GP.
Khant et al., 2017 [20]	34-year-old male with more than 86 GBCAs exposures	59 gadopentetate dimeglumine 24 gadoterate meglumine 3 gadoteridol	1.5 T	T1- hyperintensity not only in the GB, DN and pulvinar of thalamus, but also in the cortices of the pre- and post-central gyri and around the calcarine sulcus.
Kuno et al., 2017 [21]	9 pts with 1-8 CE-MRIs; 26 pts with no previous GBCA exposure.	gadopentetate dimeglumine	1.5 T	Quantitative assessment of T1 values of gray matter were significantly shorter for patients with than for patients without prior GBCA exposure.
Conte et al., 2017 [22]	18 pts included with melanoma with multiple (n=2-18) gadoxetate isodium administrations.	gadoxetate disodium	1.5 T	No significant difference in DN/pons and GP/thalamus SI; DN/pons SI and GP/thalamus. SI did not significantly increase with increasing the number of administrations.
Tedeschi et al., 2017 [24]	A 32-year old female with RRMS and 22 GDCAs exposures.	gadobutrol	1.5 T, 3.0 T, relaxometry (transverse R2* rate, longitudinal R1 relaxation rate)	Massive gadobutrol exposure did not induce significant DN relaxometry changes.
Schlemm et al., 2017 [72]	97 MS pts exclusively received either gadopentetate dimeglumine or gadobutrol.	gadopentetate dimeglumine gadobutrol	1.5 T, 3T	DN T1 hyperintensity in MS patients is associated with gadopentetate dimeglumine, but not gadobutrol.
Splendiani et al., 2018 [57]	158 MS pts received exclusively either gadoterate meglumine or gadobutrol	gadoterate meglumine gadobutrol	3.0 T	T1 hyperintensity in the DN in one-third of all patients in each group that received at least 5 GBCA administrations.
Moser et al., 2018 [25]	59 pts received only gadobutrol; 60 pts received only linear GBCAs.	gadobutrol gadoversetamide gadobenate dimeglumine, and gadodiamide	1.5 T, 3.0 T	The DN/pons SI increased in the linear GBCA group; no significant increase was seen in the gadobutrol group.

Abbreviations: GBCA: Gadolinium based contrast agents, pts: patients, CE-MRI: contrast-enhanced MRI, SI: signal intensity, DN: dentate nucleus, GP: globus pallidus, MS: multiple sclerosis, RRMS: relapsing remitting multiple sclerosis

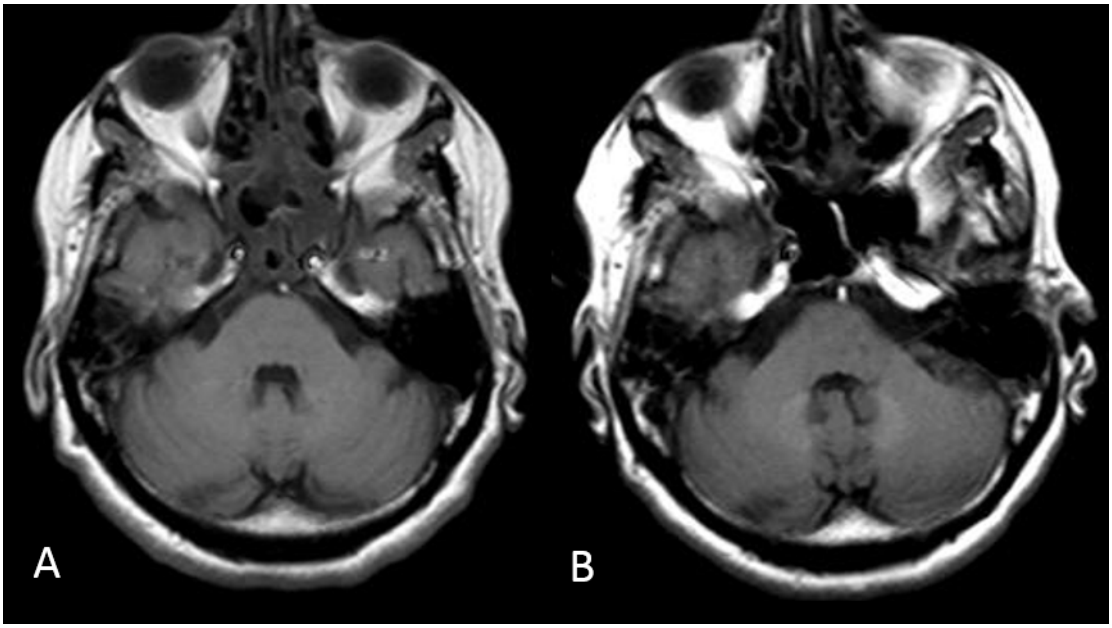

Fig. 1. *A 64 years old female with pituitary macroadenoma received 12 gadopentetate dimeglumine administrations during a period of six years. On pre-contrast T1W sequence of the last brain MRI (B) increased signal intensity in dentate nuclei bilaterally is demonstrated, compared to the respective areas of the pre-contrast T1W sequence of the first brain MRI (A) six years ago.*

the calcarine sulcus in one patient with neurofibromatosis type II and more than 86 contrast-enhanced MRI studies [20].

Subsequently, increasing evidence by other studies further confirmed the long term CNS Gd retention after the intravenous administration of various linear GBCAs, by using of qualitative [10, 11] or semiquantitative measures of T1 SI in selected regions of the brain to generate normalised SI ratios [14] or even with relaxometry [15] and quantitative analyses [21]. Of specific importance is a recent study evaluating deposition with gadoxetate disodium (the hepatocyte-specific linear GBCA used exclusively in MRI liver imaging for hepatic lesion characterisation). This study by Conte et al retrospectively reviewed data from 18 patients with stage III melanoma and multiple administrations of this linear agent and concluded that it was not associated with increased SI in DN and GB of the brain [22].

Regarding macrocyclic gadolinium chelates, many clinical studies share the common viewpoint that their use is not associated with Gd CNS deposition [7, 12, 13, 16, 23-26], probably due to higher stability comparing to linear GBCAs [54, 55]. A systematic review of 25 retrospective studies involving MRIs of 1247 patients concluded that SI within the DN and GP on unenhanced T1W MR images positively correlated with GBCAs administrations and was greater after serial administrations of linear nonionic than cyclic contrast agents [56]. On the contrary, there have been some clinical studies indicating that macrocyclic chelates also induce T1-hyperintensity in deep brain nuclei. In a study of 58 patients with relapsing-remitting multiple sclerosis (RRMS), Stojanov et al (2016) reported T1-hyperintensity in both GP and DN after multiple doses of gadobutrol, although there was no correlation between the total amount of administered gadobutrol and the increase in SI ratio of globus pallidus-to-thalamus or dentate nucleus-to-pons [17]. The SI within the GP and DN at the end of the study depended on the length of contrast administration, with the highest values of SI to be found in the group of patients receiving gadobutrol over the shortest period of time. This was thought to be the consequence of a higher contrast load and greater deposition of Gd over the shorter time. However, this study had several limitations owing to confounding factors, such as previous use of other contrast agents and the histopathologic processes in MS (accumulation of iron containing glial cells, or increased concentration of manganese and manganese-binding enzymes) that can shorten T1 relaxation time and cause brain tissue hyperintensity on T1W images [17]. Bjørnerud et al. (2017) conducted a retrospec-

Table 3. Paediatric clinical studies investigating T1 hyperintensity of the brain structures after multiple GBCAs administration.

Paediatric Studies	*Patient groups*	*Contrast agent*	*MR System field Strength*	*Results*
Miller et al., 2015[27]	8 -yrs old child who received 35 doses of linear GBCA in 12 years.	gadopentetate dimeglumine	1.5 T	Visually evident SI increase in the DN, GP, and posterior thalamus following repeated CE-MRIs.
Roberts and Holden, 2015 [28]	13-yrs old female with clival chordoma and serial follow-up CE-MRIs.	gadopentetate dimeglumine	1.5 T, 3.0 T	Hyperintensity within the DN and GP bilaterally, with the increasing use of GBCAs.
Hu et al., 2016 [29]	21 pts with multiple (5-37) CE-MRIs in the course of their medical treatment; 21 age-matched controls GBCA-naive.	gadopentetate dimeglumine	1.5 T	In all GBCA exposed pts, increased SI ratios were shown for the DN, and for the GP between the first and last MRIs.
Roberts et al., 2016 [30]	16 pts with more than 5 consecutive CE-MRIs.	gadopentetate dimeglumine	1.5 T, 3.0 T	The number of prior GBCA doses correlated significantly with progressive T1- hyperintensity in DN.
Flood et al., 2017 [31]	46 paediatric pts with at least 3 GBCA-enhanced MR examinations and 57 age-matched GBCA-naive control subjects.	gadopentetate dimeglumine	1.5 T	Increased SI within the DN, but not the GP. Significant correlation between DN SI and total cumulative gadolinium dose.
Tibussek et al., 2017 [32]	24 pts (aged 5-18 years) and subjects matched for age and sex, with non-pathologic MR neuroimaging findings (and no GBCA exposure), were included.	gadoteridol gadoterate meglumine	1.5 T	No significant differences in mean SI for any ROI and no group differences when DN-to-pons and GP-to-pulvinar ratios were compared.
Radbruch et al., 2017 [23]	41 paediatric pts (3-17 years) imaged in at least five serial CE-MRIs.	gadoterate meglumine	1.5 T	No increase of the SI in the DN was found after a mean of 8.6 serial injections of the macrocyclic agent.
Rossi et al., 2017 [33]	50 pts with normal renal function exposed to ≥6 administrations of the same macrocyclic GBCA; 59 age-matched GBCA-naive pts.	gadoterate meglumine	3.0 T	Quantitative analysis of GP/thalamus and DN/pons demonstrated a significant increase in relative SI after serial administrations of macrocyclic GBCA.
Schneider et al., 2017 [35]	34 non neurologic pts received multiple (n=5-15) doses of 0.05 mmol/kg of gadobenate; 24 control GBCA naive pts.	gadobenate	1.5 T	Multiple low-dose gadobenate exposures did not result in significantly increased mean SI in the DN, GP and thalamus.
Renz et al., 2018 [36]	2 paediatric pts cohorts who underwent at least 3 consecutive CE-MRIs.	gadopentetate dimeglumine gadobutrol	1.5 T	SI increase within the DN and GP after serial administrations of the linear agent, but not of the macrocyclic agent.

Table 3. Paediatric clinical studies investigating T1 hyperintensity of the brain structures after multiple GBCAs administration.

Paediatric Studies	*Patient groups*	*Contrast agent*	*MR System field Strength*	*Results*
Ryu et al., 2018 [37]	92 paediatric pts with at least 4 consecutive MRIs exclusively using either linear GBCA (n=41) or macrocyclic GBCA (n=51).	gadodiamide or gadopentetate dimeglumine gadoterate meglumine	1.5 T	The SI ratios of GP/thalamus and DN/pons in the linear group increased significantly between the first and last MRIs but not in the macrocyclic group.
Young et al., 2018 [38]	10 paediatric pts underwent multiple (n=4-8) gadoteridol-enhanced brain MRIs; 9 paediatric pts, each having received 6 gadodiamide-enhanced MRIs.	gadoteridol gadodiamide	1.5 T, 3.0 T	Repeat administrations of the macrocyclic agent was not associated with T1-hyperintensity in DN, while the repeat administration of the linear agent was associated with T1-hyperintensity in DN.

Abbreviations: GBCA: Gadolinium based contrast agents, pts: patients, CE-MRI: contrast-enhanced MRI, SI: signal intensity, DN: dentate nucleus, GP: globus pallidus

tive study including 17 patients with high grade gliomas and no previous history of linear GBCA administration who had received 10-44 standard doses of macrocyclic Gd-based contrast agents and reported a statistically significant and dose-dependent SI increase in the DN, although visually appreciable T1 signal hyperintensity of the dentate nucleus was found only in two patients who had received 37 and 44 standard doses, respectively [18]. Finally, a recent retrospective analysis in 158 MS patients with consecutive exclusively macrocyclic GBCAs exposures demonstrated an increase in dentate nucleus-to-pons T1 SI ratio between the first and last MRIs for both gadoterate meglumine and gadobutrol, possibly indicative of Gd retention. Visible T1 hyperintensity in the DN was noted in approximately one-third of all patients in each group that received at least five administrations of either macrocyclic GBCA [57]. To sum up, evidence to date suggests that macrocyclic GBCAs may be also responsible for Gd deposition. Still, controversy remains and findings need to be further confirmed in large cohort prospective studies.

Regarding paediatric patients, there have been many studies since 2015 that demonstrated CNS deposition patterns similar to that of adults, expressed as deep brain nuclei T1-hyperintensity, following multiple linear GBCA-enhanced MRI examinations [27-29] and not with macrocyclic agents [32, 36, 37]. One retrospective study based on quantitative evaluation of increased T1W SI in a series of 50 children with multiple previous administrations of gadoterate meglumine was the first one to implicate possible macrocyclic GBCA deposition [33]. This study received much attention, but also raised major criticism for existing inconsistencies and was not convincing [34]. One study involving paediatric patients without neurological symptoms evaluated the results of multiple serial administrations of low-dose gadobenate dimeglumine noted no SI increases indicative of gadolinium deposition and implicated that the administered dose may play a role [35]. Currently, the majority of the respective studies [23, 32, 36, 37] supports that linear GBCAs are associated with T1-hyperintensity in the brain, which is the reason for an impressive shift to macrocyclic GBCAs in paediatric MRI [58] (**Table 3**).

Evidence of gadolinium accumulation in human autopsy studies (Table 4)

T1 SI changes in deep brain nuclei are non-specific for Gd deposition and may be depicted in various metabolic and toxic pathological conditions (eg Wilson disease, hepatic encephalopathy, parenteral nutrition). Several research groups tried to prove the aetiological relationship between GBCAs exposures and T1 hyperintensity in deep brain nuclei through histologic confirmation of Gd tissue accumulation. In this context, both studies with post-mortem human tissues as well as animal studies were performed.

Table 4. Evidence of Gadolinium deposition in human autopsy studies

Study	*Patient groups*	*Contrast agent*	*Detection methods*	*Results*
McDonald et al., 2015 [48]	13 pts with more than 4 GBCA administrations; 10 pts without GBCA exposed.	gadodiamide	ICP-MS; Transmission Electron microscopy; Light microscopy	Gadolinium brain deposition in the endothelial walls and neuronal interstitium associated with GBCA administrations, independently of patients renal or hepatobiliary function.
Kanda et al., 2015 [49]	5 pts received at least 2 GBCAs; 5pts with no history of GBCAs exposure.	gadopentetate-dimeglumine gadodiamide gadoteridol	ICP-MS	Gadolinium was deposited in the brain even in subjects without severe renal dysfunction, the highest accumulation area was the DN and GP.
Murata et al., 2016 [50]	5 pts received gadoteridol; 2 pts received gadobutrol; 1 pt received gadobenate; 1 pt received gadoxetate; 9 pts without GBCAs exposure.	gadoteridol gadobutrol gadobenate gadoxetate	ICP-MS	Gadolinium was found with all agents (linear and macrocyclic) in all brain areas sampled with highest levels in GP and DN.
McDonald et al., 2017 [51]	5 pts with 4-18 GBCA administrations; 10 pts with no history of GBCAs exposure.	gadodiamide	ICP-MS; Transmission electron microscopy with energy-dispersive x-ray spectroscopy; Light microscopy	Gadolinium deposition in DN, pons, GP and thalamus, greatest in DN, in the absence of intracranial abnormalities.

Abbreviations: GBCA: Gadolinium based contrast agents, pts: patients, ICP-MS: inductively coupled plasma mass spectrometry, DN: dentate nucleus, GP: globus pallidus

In 2015, McDonald et al. used post-mortem tissue samples from the DN, pons, GP and thalamus of 23 patients with various CNS diseases (10 in contrast group, having previous multiple GBCAs exposures of gadodiamide and 13 in control group, with no previous GBCAs administrations) [48]. Gd quantification and localisation was achieved by means of inductively coupled plasma mass spectrometry (ICP-MS), transmission electron microscopy and light microscopy. They confirmed the presence of extensive Gd retention within neuronal tissues in all the sampled sites of patients in the contrast group (0.1-58.8 μg gadolinium per gram of tissue) in a significant dose-dependent relationship that correlates with unenhanced T1W hyperintensity. The majority of Gd accumulated in the endothelial walls, whereas a smaller fraction crossed an otherwise intact blood-brain barrier (BBB) and accumulated in the neural interstitium. They postulated that Gd neuronal tissue deposition exists in all patients after intravenous GBCAs administration, even in cases with normal renal and hepatobiliary function [48]. At the same year Kanda et al. once again by means of ICP-MS confirmed Gd accumulation within post-mortem brain tissues (DN, inner segment of the GP, cerebellar white matter, frontal lobe cortex, and frontal lobe white matter) of five subjects with no severe renal impairment, who had previously received both linear and macrocyclic GBCAs at least twice, with maximum

deposition levels registered in the DN and GP [49]. In both studies the specific form of Gd deposits (dissociated gadolinium ion or a chelated gadolinium compound) was not determined [48, 49].

In 2017 McDonald et al. analysed tissue samples from five patients without CNS disease and multiple (4-18) gadodiamide administrations and ten patients without Gd administrations (control group). Gd deposition occurred mainly within the endothelial wall and to a lesser extent in the neuronal interstitium (some within the neuronal cytoplasm and nucleus) with a concentration that ranged between 0.1-19.4 μg of Gd per gram of tissue. The authors suggested biologic activity of the Gd deposits, possibly from modulation of calcium channel activity or direct interaction with cellular biomolecules, but without evidence of neurotoxicity and uncertain clinical significance [51].

The first human autopsy study that compared macrocyclic and linear GBCAs was conducted in 2016 by Murata et al [50]. In their study, postmortem tissue samples obtained at multiple locations, including GP, putamen, caudate head, centrum semiovale, white matter, DN and pons were harvested from nine patients without CNS disease who received non-NSF related GBCAs (gadoteridol, gadobutrol, gadobenate, and gadoxetate) and nine patients without Gd administration. Once again Gd was detected with all agents, although in higher levels in gadodiamide and gadopentetate administration and brain areas sampled with maximum levels occurring in DN and GP. Based on their results, they suggested that Gd deposition in the brain might be unrelated to class, although comparing these data with those of Mc Donald et al. [48] Gd deposition after gadoteridol was lower than after gadodiamide.

Evidence of gadolinium accumulation in animal studies (Table 5)

Several animal imaging and autopsy studies have also been conducted to assess Gd retention in the brain after multiple administrations of different GBCAs. Robert et al evaluated the SI in the deep cerebellar nuclei (DCN) and calculated the concentration of Gd by means of ICP-MS after serial administrations of different linear and macrocyclic GBCAs in healthy rats [39, 41]. Both studies from the same research group showed that multiple injections of linear GBCAs were associated with progressive and significant T1-hyperintensity in DCN and a significant increase in the DN/cerebellar cortex ratio, as well as Gd deposition in the cerebellum, whereas no significant MRI changes were observed after macrocyclic administration. The total Gd concentration for the linear GBCAs was significantly higher compared to gadoterate meglumine or control. Jost et al, evaluated T1W SI in the DCN and GP of healthy male rats after repeated administration of both linear (gadodiamide, gadofosveset trisodium, gadopentetate dimeglumine) and macrocyclic (gadoterate meglumine, gadobutrol) GBCAs and saline [40]. The animals that were injected with linear GBCAs exhibited an increased deep cerebellar nuclei/pons SI ratio, especially with gadodiamide and gadofosveset trisodium. Macrocyclic GBCAs were not associated with observed T1 hyperintensities. At the same study increased SI of CSF spaces was observed in the post-contrast FLAIR images of all animals receiving GBCAs but not saline, indicating that all GBCAs were able to pass the blood-CSF barrier. In another study implementing ICP-MS it has been shown that a heavy increase in the Gd load from linear GBCAs may result in Gd deposition not only in the DCN, but also in cerebral cortex, subcortical brain, brainstem, olfactory bulbs and pons [42].

Lohrke et al examined the brain samples of fifty male rats after repeated linear and macrocyclic GBCAs administration. No histological changes were observed in the brain. Using laser ablation coupled with ICP-MS (LA-ICP-MS) and electron microscopy coupled to energy dispersive x-ray spectroscopy and transmission electron microscopy, high Gd concentrations in the DCN and in the granular layer of the cerebellar cortex were detected, only for linear gadodiamide and gadopentetate dimeglumine, but not for gadoteridol or gadobutrol [43]. In a study evaluating the levels of Gd present by ICP-MS in the rat brain one and 20 weeks after dosing confirmed the presence of low levels of Gd after repeated gadodiamide exposure, in a form that was cleared over time without histopathologic consequence [44]. McDonald et al. reported retained Gd in the DN, kidney, liver and spleen of adult rats at seven days post-cumulative exposure to both macrocyclic and linear GBCAs and found differences not only between the two classes of GBCAs (macrocyclic and linear) but also between GBCAs within each class, in descending order as follows: gadodiamide, gadobenate dimeglumine, gadobutrol and gadoteridol. This trend largely parallels the agents' thermodynamic stability constants. Neuronal tissue deposition of Gd appears to take place with both macrocyclic and linear GBCAs, albeit at lower concentrations than with macrocyclic agents. These findings suggest that organ tissue deposition is reduced but not eliminated following

Table 5. Evidence of Gadolinium deposition in animal studies

Study	*Patient groups*	*Contrast agent*	*Detection methods*	*Results*
Robert et al., 2015 [39]	7 rats with gadodiamide 7 rats with gadoterate meglumine 7 rats control group with saline	gadodiamide gadoterate meglumine	ICP-MS, MRI	Repeated administration of gadodiamide but not of gadoterate meglumine were associated with T1-hyperintensity in the DCN and Gd deposition in the cerebellum.
Jost et al., 2016 [40]	60 rats divided into a control and 5 GBCA groups (n=10 per group) 18 additional rats divided into 6 groups (n= 3 per group) for the evaluation of the CSF spaces	gadodiamide, gadopentetate dimeglumine gadobenate dimeglumine gadobutrol gadoterate meglumine	Brain MRI (3D-T1W, FLAIR, MR cisternography), 1.5 T	Linear, but not macrocyclic, GBCAs exhibited increased deep cerebellar nuclei/pons SI ratio. Increased SI was observed in the CSF spaces on the postcontrast FLAIR images of all animals receiving GBCAs.
Robert et al., 2016 [41]	8 rats with gadobenate dimeglumine 8 rats with gadopentetate dimeglumine 8 rats with gadodiamide 8 rats with gadoterate meglumine 8 rats control group with saline injection	gadobenate-dimeglumine gadopentetate-dimeglumine gadodiamide gadoterate-dimeglumine	ICP-MS, MRI	Linear GBCAs were associated with T1 hyperintensity in the DN along with gadolinium deposition in the cerebellum while gadoterate meglumine had no abnormal SI effect
Kartamihardja et al., 2016 [42]	23 normal mice and 26 with renal failure were divided into 4 treatment groups (gadodiamide, gadoterate meglumine, GdCl3 and saline).	gadodiamide gadoterate meglumine GdCl3	ICP-MS	In the gadodiamide group, impaired renal function increased short-term Gd retention in the liver, bone, spleen, skin, and kidney ($p<0.01$). Gadodiamide showed higher Gd retention than gadoterate meglumine. Renal function did not affect brain Gd retention.
Lohrke et al., 2017 [43]	10 rats with gadodiamide 10 rats with entetate dimeglumine 10 rats with gadobutrol 10 rats with gadoteridol 10 rats with saline as control group	gadodiamide gadopentetate-dimeglumine gadobutrol gadoteridol	ICP-MS; LA-ICP-MS; Scanning electron microscopy coupled to energy dispersive x-ray spectroscopy and transmission electron microscopy respectively	No histopathological findings were detected in the rat's brain. The administration of linear GBCAs was associated with significant higher Gd concentration in the brain compared to macrocyclic GBCA administration.
Smith et al., 2017 [44]	Treatment groups (n=6 rats per group) included low-dosage and high-dosage gadodiamide and osmolality-matched saline controls.	gadodiamide or gadopentetate dimeglumine	ICP-MS histopathology	Dose-dependent low levels of Gd were detected in the brain, 1 week after dosing. This diminished by approximately 50% 20 weeks after dosing. No histopathologic findings were associated with the levels of Gd measured.

Table 5. Evidence of Gadolinium deposition in animal studies

Study	*Patient groups*	*Contrast agent*	*Detection methods*	*Results*
McDonald et al., 2017 [45]	30 healthy rats, 6 rats in each treatment group (control, gadodiamide-exposed, gadobenate dimeglumine-exposed, gadobutrol-exposed, and gadoteridol-exposed.	gadodiamide gadobenate dimeglumine gadobutrol gadoteridol	MRI, ICP-MS Transmission Electron Microscopy	Gd deposition in brain tissue significantly varied with GBCA type. A significant positive dose-SI correlation was identified. Gd deposits were visualised in the endothelial capillary walls and neural interstitium.
Boyken et al., 2018 [46]	8 pigs received gadobutrol and gadopentetate dimeglumine. 5 received gadobutrol only.	gadobutrol gadopentetate-dimeglumine	ICP-MS	Repeated gadobutrol exposure is not associated with gadolinium deposition in healthy pigs' brain, but an additional single dose of gadopentetate dimeglumine is sufficient for gadolinium accumulation in the DN and GP.
Rasschaert et al., 2018 [47]	5/6th subtotally nephrectomised female rats.	gadoterate meglumine gadobenate dimeglumine gadodiamide	ICP-MS, MRI	Very low levels or absence of Gd after repeated injections of gadoterate in renally impaired rats, in contrast to the 2 linear GBCAs, for which the highest total Gd concentration was demonstrated in the DCNs.
Bussi et al., 2018 [69]	5 male and 5 female juvenile rats.	gadobenate dimeglumine	ICP-MS, histopathology	Decrease of up to 4.5-fold in Gd content in the cerebral cortex and cerebellum but less so in the subcortical brain following the 60-day treatment-free recovery period. No evidence of microscopic findings or behavioural or neurological effects related to potential Gd presence in the brain.

Abbreviations: GBCA: Gadolinium based contrast agents, ICP-MS: inductively coupled plasma mass spectrometry, LA- ICP-MS: laser ablation coupled with inductively coupled plasma mass spectrometry, SI: signal intensity, DCN: deep cerebellar nuclei, DN: dentate nucleus, GP: globus pallidus

administration of macrocyclic GBCAs [45]. In a study involving healthy pigs it was demonstrated that multiple exposures to gadobutrol is not associated with Gd deposition in brain tissue whereas a single additional administration of linear GBCA sufficed for retention in the DN and GP [46]. A more recent study in rats with impaired renal function, minimal gadoterate meglumine levels were detected in the brain with no T1 hyperintensity of the DCN, whereas marked Gd retention was observed in almost all brain areas after injections of linear GBCAs (gadobenate dimeglumine and gadodiamide [47].

Suggested Mechanisms of GBCAs entering the brain parenchyma

The CNS environment equilibrium is strictly regulated by the BBB and the blood-cerebrospinal fluid (CSF) barrier (BCSFB) [59] which may at times be compromised due to pathological changes. However, the exact mechanisms of GBCAs biodistribution are not well-known and it has been postulated that, even under normal homeostasis, GBCAs

may be allowed to enter CSF crossing the intact BBB [60]. In a study involving healthy rats, where the penetration and distribution of different GBCAs (gadopentetate dimeglumine, gadobenate dimeglumine, gadodiamide, gadoterate meglumine, gadobutrol) into the CSF and parenchyma was evaluated, there has been evidence supporting the notion that the GBCAs distributed with the CSF flow might represent potential pathway of infiltration into the brain tissue, regardless of GBCA structure and physicochemical properties [40].

In concert with a relatively new concept of the existence of a paravascular fluid system for CSF and interstitial fluid (ISF) exchange in the brain, Oner et al. demonstrated T1 signal hyperintensity of the DN nucleus and GP following intrathecal injection of a linear GBCA, based on visual and quantitative analysis [61]. The agent was directly introduced in the subarachnoid space with no intravenous injection and therefore without crossing the BBB, thus suggesting entry via this pathway named the "glymphatic" system [60]. Moreover, it is well-known that the deep cerebellar nuclei, proximal to the cerebellar parenchyma of the fourth ventricle, are particularly rich in metals (eg iron, copper and zinc) [62]. Given the fact that the local accumulation in the DCN could be the result of a competition between local endogenous metals and Gd, other speculated possible mechanisms comprise transmetallation and/or specific metal transporters [55, 63, 64]. In the end, the functional role of brain barriers and fluid distribution and exchange in the CNS, both in sickness and in health, remain obscure and need to be further studied, in order to enlighten the pathophysiologic mechanisms of gadolinium deep brain nuclei retention [64].

Clinical and biological impacts of GBCAs administrations

Although there is robust, convincing evidence of Gd deposition in the brain after repeated GBCAs administrations, the clinical impact of such a phaenomenon has not been evaluated in depth. Apart from adverse effects, no strong evidence exists that CNS gadolinium retention may promote significant biological or clinical effects. In patients with renal insufficiency and more than two exposures of gadodiamide, spurious hypocalcaemia was demonstrated [65]. A study by Burke et al. described patients' self-reported toxicity potentially related to GBCAs administrations. Fifty subjects with normal renal function completed a questionnaire for symptoms attributed to Gd toxicity [66]. Complaints comprised bone/joint pain and head/neck symptoms such as vision, headache and hearing change.

In a large population-based study Welk et al. investigated the relationship between parkinsonism and gadolinium exposure [67]. In this study, 246557 patients underwent at least one MRI examination during the study. Of them, 99739 patients received at least one dose of gadolinium and 2446 patients underwent four or more CE-MRI examinations. No significant association between Gd exposure and parkinsonism was exhibited, rejecting the hypothesis that Gd deposits in the GP lead to neuronal damage manifesting as parkinsonism. In another retrospective study ten patients who had previously received more than 20 exposures of gadoterate were assessed for potential clinical cerebellar syndrome. During the 91-month follow-up, no signs suggesting cerebellar toxicity were reported by the clinician [68]. However, further studies are required to search for other non-specific symptoms (pain, cognitive changes) after Gd exposure.

Finally, in a study involving juvenile rats that received either saline or gadobenate dimeglumine in order to determine the impact of single and cumulative doses on tissue Gd presence measured by ICP-MS, as well as on behaviour and neurological function, no effects on behaviour or cognitive were noted, even for the highest administered cumulative dose (15 mmol/kg), corresponding to about 25 injections of the standard dose in humans. Gd presence was variable across tissues and decreased during the 60-day treatment-free period [69]. They concluded that Gd presence in juvenile rat brain following single or repeated gadobenate dimeglumine administrations was minimal, with no neurotoxicity effects noted.

Potential associated confounding factors in the assessment of gadolinium CNS deposition

Most patients undergoing repeated GBCA-enhanced brain MR examinations have an established or suspected neurological disease. Therefore, the BBB is considered compromised to a variable extent by disease processes (inflammation) and/or treatments (radiation therapy, steroids, chemotherapy) that potentially permit the GBCAs passage and represent confounding factors. Even more, MS and brain tumours have also been related to signal intensity changes in brain parenchyma.

Previous studies have linked DN SI increases and secondary progressive MS [70], thereafter patients with MS

have been excluded from most studies related to CNS Gd deposition. Stojanov et al., in their study involving patients with RRMS who had repeated administrations of gadobutrol, advocated greater T1 hyperintensity in the DN and the GP with serial administrations over a shorter time period than over a longer time period [17]. This finding was debated by Agris et al. who raised questions concerning whether disease activity is a confounding factor for inducing or even enabling Gd accumulation [71]. However, a study that used quantitative relaxometry and multivariate regression analysis in 74 patients with RRMS concluded that T1 hyperintensity is independent of disease duration or severity. Findings of signal intensity changes in DBN were positive even after exclusion of patients with MS lesions near the DN [15]. Similarly, in a cohort study of 97 MS patients DN T1 hyperintensity was associated with Gd-DTPA (but not Gd-BT-DO3A) administrations, regardless of disease duration and severity [72].

Concerning radiation induced brain injury, it is well known that it may produce CNS calcifications in childhood, presenting as T1 parenchymal hyperintensity [73]. In a paediatric study by Tamrazi et al. 144 patients with GBCA enhanced MR examinations were analysed and results demonstrated that signal hyperintensities of the DN and GP do occur in patients with brain tumours undergoing CNS irradiation, as well as in patients with untreated primary brain tumours, independent of GBCA exposures. However, at multiple GBCAs administrations (≥20 times), Gd deposition seemed to contribute more to signal intensity increase [74]. A recent study data analysis including 44 patients treated with radiation therapy for supratentorial glioblastoma who underwent pre- and post-radiation brain MRIs and relaxometry showed T1 hyperintensity in the brain parenchyma, possibly associated with accelerated Gd deposition due to blood-brain barrier impairment [75].

GBCAs chelates are eliminated from the body primarily by renal and secondarily by biliary excretion [76]. Since the first reports, it became evident that Gd CNS deposition occurs even with normal renal function. However it was recently supported that the rate of deposition may be affected by chronic kidney disease as suggested by the results of a comparative study of 13 patients on chronic haemodialysis and 13 patients with normal renal function with multiple gadoversetamide administrations [77].

Recommendations

In 2017, the US Food and Drug Administration (FDA) examined available evidence about the GBCAs related depositions as part of surveilling post-release drug safety. They considered that linear Gd chelates may show greater propensity for retention in the body than macrocyclic ones and recommended evaluation of the characteristics of each agent when administering GBCAs in patients at higher risk for deposition or those who may require repeated contrast-enhanced MRIs to monitor a chronic condition. The FDA also stated as "a class-wide warning about Gd retention in the labeling of GBCAs and a new guide that should be presented to patients in advance of receiving a GBCA" [78].

Following the FDAs Safety Announcement, the International Society of Magnetic Resonance in Medicine (ISMRM) Safety Committee maintained that to-date no adverse health effects related to the Gd retention in the brain have been demonstrated following studies in humans and animal studies [2]. However, a set of recommendations for the safe use of GBCAs were issued by the organisation urging towards a judicious use of Gd chelates, only when necessary. Since, GBCAs have an established role for disease diagnosis and treatment monitoring, they should be administered when indicated for diagnostic purposes, with documented associated medical information in the patient's records. Concerning the choice of a specific agent it is stated that "many factors that should be evaluated including pharmacokinetics, relaxivity, efficacy, potential or real side-effects (eg allergic reactions), patient age, the need for repeat examinations, and cost".

Following a review carried out by the Pharmacovigilance Risk Assessment Committee (PRAC) with associated recommendations, the European Medicines Agency (EMA) confirmed restrictions on using linear Gd agents. They proposed that the use of all intravenous linear GBCAs (gadodiamide, gadopentetic acid and gadoversetamide) should be suspended in the EU with few exceptions. Gadobenic acid and gadoxetic acid should be maintained with a limited use for liver examination, provided there is a relative indication. Gadopentetic acid should only be applied for intra-articular use. Macrocyclic agents (gadobutrol, gadoteric acid and gadoteridol) were considered more stable with a lower propensity to release gadolinium than linear agents. These products were allowed to be used in their current indications but in the lowest possible doses to suffice for diagnostic purposes [54, 79]. Subsequently, new concepts have begun to emerge concerning screening practices which may also be modified in an attempt

to minimise dose or repeat contrast-enhanced MR examinations [80].

Conclusion

Considerable evidence suggests that repeated administrations of GBCAs lead to accumulation of Gd in brain parenchyma and mainly in the deep brain nuclei. The mechanisms for Gd retention have yet to be elucidated and, although there are differences amongst the agents' categories, data is conflicting. Although linear GBCAs have been primarily accused and subsequently suspended at least in Europe, there is no doubt that repeating administration of macrocyclic GBCA could also lead to Gd deposition in brain parenchyma. Of note is the fact that, to-date, there are no related brain histopathological changes and the exact clinical or biological importance of this deposition remains unknown. Further research is needed to elucidate the mechanisms of Gd deposition in the brain, investigate the associated biological effect or clinical impact and determine possible effects in behaviour and cognition. **R**

Conflict of interest

The authors declared no conflicts of interest.

References

1. Runge VM, Carollo BR, Wolf CR, et al. Gd DTPA: a review of clinical indications in central nervous system magnetic resonance imaging. *Radiographics* 1989; 9(5): 929-958.
2. Gulani V, Calamante F, Shellock FG, et al. Gadolinium deposition in the brain: summary of evidence and recommendations. *Lancet Neurol* 2017; 16(7): 564-570.
3. Marckmann P, Skov L, Rossen K, et al. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol* 2006; 17(9): 2359-2362.
4. Daftari Besheli L, Aran S, Shaqdan K, et al. Current status of nephrogenic systemic fibrosis. *Clin Radiol* 2014; 69(7): 661-668.
5. 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(3): 834-841.
6. 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: 685-690.
7. 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(3): 783-791.
8. Ramalho J, Castillo M, AlObaidy M, et al. High signal intensity in globus pallidus and dentate nucleus on unenhanced T1-weighted MR images: evaluation of two linear gadolinium-based contrast agents. *Radiology* 2015; 276(3): 836-844.
9. 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(7): 470-472.
10. Weberling LD, Kieslich PJ, Kickingereder P, et al. Increased signal intensity in the dentate nucleus on unenhanced T1-weighted images after gadobenate dimeglumine administration. *Invest Radiol* 2015; 50(11): 743-748.
11. Adin ME, Kleinberg L, Vaidya D, et al. Hyperintense dentate nuclei on T1-weighted MRI: Relation to repeat gadolinium administration. *Am J Neuroradiol* 2015; 36(10): 1859-1865.
12. 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(3): 803-809.
13. Radbruch A, Weberling LD, Kieslich PJ, et al. Gado-

linium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. *Radiology* 2015; 275(3): 783-791.
14. Ramalho J, Semelka RC, AlObaidy M, et al. Signal intensity change on unenhanced T1-weighted images in dentate nucleus following gadobenate dimeglumine in patients with and without previous multiple administrations of gadodiamide. *Eur Radiol* 2016; 26(11): 4080-4088.
15. Tedeschi E, Palma G, Canna A, et al. In vivo dentate nucleus MRI relaxometry correlates with previous administration of Gadolinium-based contrast agents. *Eur Radiol* 2016; 26(12): 4577-4584.
16. 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(11): 683-690.
17. Stojanov DA, Aracki-Trenkic A, Vojinovic S, et al. Increasing signal intensity within the dentate nucleus and globus pallidus on unenhanced T1W magnetic resonance images in patients with relapsing-remitting multiple sclerosis: correlation with cumulative dose of a macrocyclic gadolinium-based contrast age. *Eur Radiol* 2016; 26(3): 807-815.
18. Bjørnerud A, Vatnehol SAS, Larsson C, et al. Signal enhancement of the dentate nucleus at unenhanced MR imaging after very high cumulative doses of the macrocyclic gadolinium-based contrast agent gadobutrol: an observational study. *Radiology* 2017; 285(2): 434-444.
19. Zhang Y, Cao Y, Shih GL, et al. Extent of signal hyperintensity on unenhanced T1-weighted Brain MR images after more than 35 administrations of linear gadolinium-based contrast agents. *Radiology* 2017; 282(2): 516-525.
20. Khant ZA, Hirai T, Kadota Y, et al. Shortening in the cerebral cortex after multiple administrations of gadolinium-based contrast agents. *Magn Reson Med Sci* 2017; 16(1): 84-86.
21. Kuno H, Jara H, Buch K, et al. Global and regional brain assessment with quantitative MR imaging in patients with prior exposure to linear gadolinium-based contrast agents. *Radiology* 2017; 283(1): 195-204.
22. Conte G, Preda L, Cocorocchio E, et al. Signal intensity change on unenhanced T1-weighted images in dentate nucleus and globus pallidus after multiple administrations of gadoxetate disodium: an intraindividual comparative study. *Eur Radiol* 2017; 27(10): 4372-4378.
23. Radbruch A, Haase R, Kickingereder P, et al. Pediatric Brain: no increased signal intensity in the dentate nucleus on unenhanced T1-weighted MR images after consecutive exposure to a macrocyclic gadolinium-based contrast agent. *Radiology* 2017; 283(3): 828-836.
24. Tedeschi E, Cocozza S, Borrelli P, et al. Longitudinal assessment of dentate nuclei relaxometry during massive gadobutrol exposure. *Magn Reson Med Sci* 2018; 17(1): 100-104.
25. Moser FG, Watterson CT, Weiss S, et al. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: Comparison between gadobutrol and linear gadolinium-based contrast agents. *AJNR Am J Neuroradiol* 2018; 39(3): 421-426.
26. Eisele P, Alonso A, Szabo K, et al. Lack of increased signal intensity in the dentate nucleus after repeated administration of a macrocyclic contrast agent in multiple sclerosis. An observational study. *Medicine* (Baltimore) 2016; 95(39): e4624.
27. Miller JH, Hu HH, Pokorney A, et al. MRI brain signal intensity changes of a child during the course of 35 gadolinium contrast examinations. *Pediatrics* 2015; 136(6): e1637-1640.
28. Roberts DR, Holden KR. Progressive increase of T1 signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images in the pediatric brain exposed to multiple doses of gadolinium contrast. *Brain Dev* 2016; 38(3): 331-336.
29. Hu HH, Pokorney A, Towbin RB, et al. Increased signal intensities in the dentate nucleus and globus pallidus on unenhanced T1-weighted images: evidence in children undergoing multiple gadolinium MRI exams. *Pediatr Radiol* 2016; 46(11): 1590-1598.
30. Roberts DR, Chatterjee AR, Yazdani M, et al. Pediatric patients demonstrate progressive T1 weighted hyperintensity in the dentate nucleus following multiple doses of gadolinium-based contrast agent. AJNR *Am J Neuroradiol* 2016; 37(12): 2340-2347.
31. Flood TF, Stence NV, Maloney JA, et al. Pediatric brain: repeated exposure to linear gadolinium-based contrast material is associated with increased signal intensity at unenhanced T1-weighted MR imaging.

Radiology 2017; 282(1): 222-228.
32. Tibussek D, Rademacher C, Caspers J, et al. Gadolinium brain deposition after macrocyclic gadolinium administration: a pediatric case-control study. *Radiology* 2017; 285(1): 223-230.
33. Rossi Espagnet MC, Bernardi B, Pasquini L, et al. Signal intensity at unenhanced T1-weighted magnetic resonance in the globus pallidus and dentate nucleus after serial administrations of a macrocyclic gadolinium-based contrast agent in children. *Pediatr Radiol* 2017; 47(10): 1345-1352.
34. Lancelot E, Raynaud JS, Desché P. Lack of evidence of a relationship between magnetic resonance signal intensity changes in the globus pallidus and dentate nucleus, and repeated administrations of gadoterate meglumine in children. *Pediatr Radiol* 2017; 47(12): 1692-1693.
35. Schneider GK, Stroeder J, Roditi G, et al. T1 signal measurements in pediatric brain: Findings after multiple exposures to gadobenate dimeglumine for imaging of nonneurologic disease. *AJNR Am J Neuroradiol* 2017; 38(9): 1799-1806.
36. Renz DM, Kümpel S, Böttcher J, et al. Comparison of unenhanced T1-weighted signal intensities within the dentate nucleus and the globus pallidus after serial applications of gadopentetate dimeglumine versus gadobutrol in a pediatric population. *Invest Radiol* 2018; 53(2): 119-127.
37. Ryu YJ, Choi YH, Cheon JE, et al. Pediatric brain: gadolinium deposition in dentate nucleus and globus pallidus on unenhanced T1-weighted images is dependent on the type of contrast agent. *Invest Radiol* 2018; 53(4): 246-255.
38. Young JR, Orosz I, Franke MA, et al. Gadolinium deposition in the paediatric brain: T1-weighted hyperintensity within the dentate nucleus following repeated gadolinium-based contrast agent administration. *Clin Radiol* 2018; 73(3): 290-295.
39. Robert P, Lehericy S, Grand S, et al. T1-weighted hypersignal in the deep cerebellar nuclei after repeated administrations of gadolinium-based contrast agents in healthy rats: difference between linear and macrocyclic agents. *Invest Radiol* 2015; 50(8): 473-480.
40. Jost G, Lenhard DC, Sieber MA, et al. Signal increase on unenhanced T1-weighted images in the rat brain after repeated, extended doses of gadolinium-based contrast agents comparison of linear and macrocyclic agents. *Invest Radiol* 2016; 51(2): 83-89.
41. Robert P, Violas X, Grand S, et al. Linear gadolinium-based contrast agents are associated with brain gadolinium retention in healthy rats. *Invest Radiol* 2016; 51(2): 73-82.
42. Kartamihardja AAP, Nakajima T, Kameo S, et al. Distribution and clearance of retained gadolinium in the brain: Differences between linear and macrocyclic gadolinium based contrast agents in a mouse model. *Br J Radiol* 2016; 89(1066): 20160509.
43. Lohrke J, Frisk AL, Frenzel T, et al. Histology and gadolinium distribution in the rodent brain after the administration of cumulative high doses of linear and macrocyclic gadolinium-based contrast agents. *Invest Radiol* 2017; 52(6): 324-333.
44. Smith APL, Marino M, Roberts J, et al. Clearance of gadolinium from the brain with no pathologic effect after repeated administration of gadodiamide in healthy rats: an analytical and histologic study. *Radiology* 2017; 282(3): 743-751.
45. McDonald RJ, McDonald JS, Dai D, et al. Comparison of gadolinium concentrations within multiple rat organs after intravenous administration of linear versus macrocyclic gadolinium chelates. *Radiology* 2017; 285(2): 536-545.
46. Boyken, J, Frenzel T, Lohrke J, et al. Gadolinium accumulation in the deep cerebellar nuclei and globus pallidus after exposure to linear but not macrocyclic gadolinium-based contrast agents in a retrospective pig study with high similarity to clinical conditions. *Invest Radiol* 2018; 53(5): 278-285.
47. Rasschaert M, Emerit A, Fretellier N, et al. Gadolinium retention, brain T1 hyperintensity, and endogenous metals: a comparative study of macrocyclic versus linear gadolinium chelates in renally sensitized rats. *Invest Radiol* 2018; 53(6): 328-337.
48. McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. *Radiology* 2015; 275(3): 772-782.
49. 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: 228-232.
50. Murata N, Gonzalez-Cuyar LF, Murata K, et al. Macrocyclic and other non-group 1 gadolinium contrast

agents deposit low levels of gadolinium in brain and bone tissue: Preliminary results from 9 patients with normal renal function. *Invest Radiol* 2016; 51(7): 447-453.
51. McDonald RJ, McDonald JS, Kallmes DF, et al. Gadolinium deposition in human brain tissues after contrast-enhanced MR imaging in adult patients without intracranial abnormalities. *Radiology* 2017; 285(2): 546-554.
52. Rogosnitzky M and Branch S. Gadolinium-based contrast agent toxicity: a review of known and proposed mechanisms. *Biometals* 2016; 29: 365-376.
53. 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(12): 817-828.
54. Dekkers IA, Roos, R, Van AD. Gadolinium retention after administration of contrast agents based on linear chelators and the recommendations of the european medicines agency. *Eur Radiol* 2017; 28: 1579-1584.
55. Port M, Idée J-M, Medina C, et al. Efficiency, thermodynamic and kinetic stability of marketed gadolinium chelates and their possible clinical consequences: a critical review. *BioMetals* 2008; 21(4): 469-490.
56. Olchowy C, Cebulski K, Łasecki M, et al. The presence of the gadolinium-based contrast agent depositions in the brain and symptoms of gadolinium neurotoxicity-A systematic review. *PLoS One* 2017; 12(2): 1-14.
57. Splendiani A, Perri M, Marsecano C, et al. Effects of serial macrocyclic-based contrast materials gadoterate meglumine and gadobutrol administrations on gadolinium-related dentate nuclei signal increases in unenhanced T1-weighted brain: a retrospective study in 158 multiple sclerosis (MS) patients. *Radiol Medica* 2018; 123(2): 125-134.
58. Update on FDA approach to safety issue of gadolinium retention after administration of gadolinium-based contrast agents. https://www.fda.gov/Drugs/DrugSafety/ucm589213.htm. Accessed March 3, 2019.
59. Engelhardt B, Sorokin L. The blood-brain and the blood-cerebrospinal fluid barriers: Function and dysfunction. *Semin Immunopathol* 2009; 31(4): 497-511.
60. Taoka T, Naganawa S. Gadolinium-based contrast media, cerebrospinal fluid and the glymphatic system: possible mechanisms for the deposition of gadolinium in the brain. *Magn Reson Med Sci* 2018; 17(2): 111-119.
61. Öner AY, Barutcu B, Aykol S, et al. Intrathecal contrast-enhanced magnetic resonance imaging-related brain signal changes: residual gadolinium deposition? *Invest Radiol* 2017; 52(4): 195-197.
62. Popescu BFG, Robinson CA, Rajput A, et al. Iron, copper, and zinc distribution of the cerebellum. *Cerebellum* 2009; 8(2): 74-79.
63. Tedeschi E, Caranci F, Giordano F, et al. Gadolinium retention in the body: what we know and what we can do. *Radiol Medica* 2017; 122(8): 589-600.
64. McDonald RJ, Levine D, Weinreb J, et al. Gadolinium retention: a research roadmap from the 2018 NIH/ACR/RSNA workshop on gadolinium chelates. *Radiology* 2018; 289(2): 517-534.
65. Prince MR, Zhang H, Zou Z, et al. Incidence of immediate gadolinium contrast media reactions. *AJR Am J Roentgenol* 2011; 196(2): 138-143.
66. Burke LMB, Ramalho M, AlObaidy M, et al. Self-reported gadolinium toxicity: A survey of patients with chronic symptoms. *Magn Reson Imaging* 2016; 34(8): 1078-1080.
67. Welk B, McArthur E, Morrow SA, et al. Association between gadolinium contrast exposure and the risk of parkinsonism. *JAMA* 2016; 316(1): 96-98.
68. Perrotta G, Metens T, Absil J, et al. Absence of clinical cerebellar syndrome after serial injections of more than 20 doses of gadoterate, a macrocyclic GBCA: a monocenter retrospective study. *J Neurol* 2017; 264(11): 2277-2283.
69. Bussi S, Coppo A, Botteron C, et al. Differences in gadolinium retention after repeated injections of macrocyclic MR contrast agents to rats. *J Magn Reson Imaging* 2018; 47(3): 746-752.
70. 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(2): 503-510.
71. Agris J, Pietsch H, Balzer T. What evidence is there that gadobutrol causes increasing signal intensity within the dentate nucleus and globus pallidus on unenhanced T1W MRI in patients with RRMS? *Eur Radiol* 2016; 26: 816-817.

72. Schlemm L, Chien C, Bellmann-Strobl J, et al. Gadopentetate but not gadobutrol accumulates in the dentate nucleus of multiple sclerosis patients. *Mult Scler J* 2017; 23(7): 963-972.
73. Suzuki S, Nishio S, Takata K, et al. Radiation-induced brain calcification: Paradoxical high signal intensity in T1-weighted MR images. *Acta Neurochir* (Wien) 2000; 142(7): 801-804.
74. Tamrazi B, Nguyen B, Liu C-SJ, et al. Changes in Signal intensity of the dentate nucleus and globus pallidus in pediatric patients: impact of brain irradiation and presence of primary brain tumors independent of linear gadolinium-based contrast agent administration. *Radiology* 2018; 287(2): 452-460.
75. Lim WH, Choi SH, Yoo RE, et al. Does radiation therapy increase gadolinium accumulation in the brain? Quantitative analysis of T1 shortening using R1 relaxometry in glioblastoma multiforme patients. *PLoS One* 2018; 13(2): e 0192838.
76. Aime S, Caravan P. Biodistribution of gadolinium-based contrast agents, including gadolinium deposition. *J Magn Reson Imaging* 2009; 30(6): 1259-1267.
77. Rahatli FK, Donmez FY, Kibaroglu S, et al. Does renal function affect gadolinium deposition in the brain? *Eur J Radiol* 2018; 104: 33-37.
78. U.S. Food and Drug Administration. (2017). FDA Warns that Gadolinium based contrast agents (gbcas) are retained in the body; Requires new class warnings. https://www.fda.gov/downloads/Drugs/DrugSafety/ UCM589442. Accessed March 3 2019.
79. European Medicines Agency (2017). EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2017/07/WC500231829.pdf. Accessed October 23 2018.
80. Vergauwen E, Vanbinst AM, Brussaard C, et al. Central nervous system gadolinium accumulation in patients undergoing periodical contrast MRI screening for hereditary tumor syndromes. *Hered Cancer Clin Pract* 2018; 16(1): 2.

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