Chapter

Current Clinical Issues: Deposition of Gadolinium Chelates

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Abstract

Clinically available gadolinium chelate-based contrast agents (GBCAs) are divided into two groups by chelate types: linear GBCAs and macrocyclic GBCAs. The characteristic features of GBCAs are introduced in this chapter. Currently, there are two clinical issues related to the administration of GBCAs: nephrogenic systemic fibrosis (NSF) and brain deposition of gadolinium. NSF occurs in patients with chronic renal failure who had magnetic resonance imaging (MRI) examinations with GBCA injections. Frequent administrations would induce NSF, and GBCA stability would be discussed in this chapter. Linear GBCAs are more likely to be deposited in brain tissues than macrocyclic GBCAs. We present the trend of GBCA deposition or retention with our published research studies with our previous researches. We have investigated the effect of GBCAs deposited in the brain for infants.

Keywords: gadolinium-based contrast agent, nephrogenic systemic fibrosis, linear chelates, macrocyclic chelates, gadolinium brain deposition

1. Introduction

1.1 Development history

Magnetic resonance imaging (MRI) is a powerful cross-sectional diagnostic imaging modality. Its technical principle developed by Bloch and Purcell was advanced for clinical application since 1973 by Lauterbur and Mansfield [1]. MRI allows a generation of noninvasive images and a determination of detailed internal morphology and function of organs and tissues, rendering it particularly useful for detection and characterization of diseased soft tissue including solid tumors. MRI has many advantages such as the absence of ionizing radiation exposure and provides three-dimensional images with high spatial resolution and contrast. The quality of MR images, including spatial resolution, signal-to-noise ratio, and contrast-to-noise ratio (CNR), has been markedly improved in the past decades. In addition, the use of contrast agents (CAs) has been playing a crucial role in improving the detection of tumor lesions, especially brain tumors, due to a rupture of blood-brain barrier by enhancing the image contrast between normal and abnormal tissues [2, 3].

1.2 Contrast mechanism

CAs in the field of MRI alter the longitudinal (T1) and transverse (T2) relaxation rates of the surrounding water protons, therefore enhancing the image

contrast in tissue of interest [4]. MRI CAs generally behave as positive CAs on T1-weighted image (T1WI) or negative CAs on T2WI based on their relaxation mechanisms. Gadolinium-based contrast agents (GBCAs) are commonly used as T1 contrast agents that have the ability to decrease T1 relaxation times of protons and work as a positive image contrast on T1WI. GBCAs have been commercially introduced since 1988 and have been globally used for more than 25 years in more than 100 million patients, and over 10 million contrast-enhanced MRI scans were annually performed [5]. These agents distribute into plasma, interstitial spaces, and extracellular spaces immediately after intravenous injection. Since most GBCAs are employed as extracellular agents, dynamic study of MRI has been performed to detect hypervascular tumors, such as hepatocellular carcinoma. The extracellular distribution of GBCAs is most effective in detection and diagnosis of disrupted blood-brain barrier in the central nervous system such as multiple sclerosis and brain tumor [6, 7].

1.3 Relaxivity

The relaxation of solvent nuclei around paramagnetic center has been described by Solomon, Bloembergen, and others [8]. Every material has proper T1 and T2 relaxation rates (1/T1, 1/T2) of water protons, and the difference of relaxivities produces the contrasts among tissues. The use of BCAs can increase both T1 and T2 relaxation rates (1/T1, 1/T2) of water protons. The observed water proton relaxation rates contribute to the contrast of the relaxation rates (1/T1, 1/T2) without GBCAs, and the increased relaxation rates (1/T1, 1/T2) are promoted using GBCAs. The increased relaxation rates of water protons are linearly related to the concentration of GBCAs within the range of clinically relevant concentrations. The relaxivity is defined as a concentration-dependent increase in relaxation rate of water protons by GBCAs in the units of $mM^{-1}\ s^{-1}$ [2].

$$(1/T1,2)obs = (1/T1,2)d + r1,2\ [Gd] \quad (1)$$

Protein-binding GBCAs, Gd-BOPTA (MultiHance), Gd-EOB-DTPA (Eovist), and MS-325 (Ablaber), have increased relaxivity in plasma because of their non-covalent binding to albumin which slows down the molecular rotation [2, 8]. In particular, MS-325 has an r1 relaxivity as high as 28 ± 1 $mM^{-1}\ s^{-1}$ when measured at 0.47 T and 37°C in plasma [9].

1.4 Safety

Safety of GBCAs for clinical applications is another critical issue because of the reported harmful effects of Gd^{3+} in patients. Gd^{3+} ions are highly toxic in ionic form due to interference with calcium channel and protein-binding sites. This is because the ionic radius of Gd^{3+} ions is almost equal to that of Ca^{2+} and Gd^{3+} can compete with Ca^{2+} and cause toxic side effects for the biological system. Free Gd^{3+} ions accumulate in the spleen, liver, bone, and kidney, and LD50 of free Gd^{3+} ion is 0.2 mmol kg^{-1} in mice. To prevent the toxicity of Gd^{3+} ions, chelate ligands are employed to reduce free Gd^{3+} ions. Harmful Gd^{3+} ions may still be released from some type of chelates. The mechanism of release of free Gd^{3+} from chelated CAs has been investigated. One of the hypotheses is transmetallation with other metal ions, including Zn^{2+}, Ca^{2+}, and Cu^{2+} in the serum of human body. Another hypothesis is the protonation of the ligands at low pH. These factors would cause chelate dissociation in vivo [10]. Therefore, gadolinium chelate-based MRI CAs emerged for their good safety profiles and the stability for high thermodynamic and kinetic stability.

The GBCAs are excreted from the kidney within hours after intravenous administration [11]. GBCAs are ultimately eliminated through the renal route with half-lives of 1–2 h and excreted intact in urine (more than 95% of the injected dose in 24 h). The dose of these small molecular GBCAs in clinical use is usually 100 times lower than their LD50. GBCAs used to be used as a contrast agent of MRI even for patients with chronic kidney disease (CKD). However, in 2006, nephrogenic systemic fibrosis (NSF) was reported by Grobner. Many papers reported that CKD might be the main factor of NSF [12, 13]. These days, GBCAs are not used for patients with CDK.

2. Chelate types of gadolinium-based contrast agent

GBCAs are categorized mainly into two groups: linear and macrocyclic GBCAs. In general, macrocyclic GBCAs are more stable than linear GBCAs due to higher thermodynamic and kinetic stability (**Tables 1–4**) [14, 15]. In clinical use, gadopentetate dimeglumine, Gd-DTPA (Magnevist); gadoterate, Gd-DOTA (Dotarem); gadoteridol, Gd-HP-DO3A (ProHance); and gadodiamide, Gd-DTPA-BMA (Omniscan) have similar r1 relaxivity in the range of 3.5–3.8 mM^{-1} s^{-1} (20 MHz and 37°C) (**Tables 1–4**).

2.1 Linear chelates

Gadolinium-DTPA: Gadopentetate dimeglumine, Gd-DTPA (Magnevist), is one of the linear-type chelating agents. Gd3+ ions are covered by the polydentate ligand like a claw (**Figure 1**). The toxicity of Gd-DTPA is more than tenfold lower than the toxicity of Gd3+ ion and DTPA as a ligand. Its safety profile is very well established with low incidence of adverse effects. The risk of adverse reactions is low when then agent is administrated intravenously even up to doses of 0.03 mol/kg.

Commercial name	Chemical name	Structure	Chelate type
Magnevist	Gadopentetate dimeglumine	Gd-DTPA	Linear
Omniscan	Gadodiamide	Gd-DTPA-BMA	Linear
Dotarem	Gadoterate meglumine	Gd-DOTA	Macrocyclic
ProHance	Gadoteridol	Gd-HP-DO3A	Macrocyclic
Gadovist	Gadobutrol	Gd-DO3A-butrol	Macrocyclic

Table 1.
Representative clinical gadolinium-based contrast agents (GBCAs).

GBCAs	LD_{50} (mmol/kg)	References
Gd-DTPA	8	[16]
Gd-DTPA-BMA	25	[18]
Gd-DOTA	18	[17]
Gd-HP-DO3A	<15	[19]
Gd-DO3A-butrol	25	[18]

GBCA, Gadolinium-based contrast agent; LD_{50}, median lethal dose.

Table 2.
Acute intravenous toxicity in rats [14].

GBCAs	Concentration (mmol/l)	Osmolality (osmol/kgH_2O)	Viscosity	References
Gd-DTPA	0.5	1.96	2.9	[20]
Gd-DTPA-BMA	0.5	0.79	1.4	[18, 20]
	1.0	1.90	3.9	[19]
Gd-DOTA	0.5	1.35	2.0	[19]
	1.0	4.02	11.3	[19]
Gd-HP-DO3A	0.5	0.63	1.3	[19]
	1.0	1.91	3.9	[19]
Gd-DO3A-butrol	0.5	0.57	1.4	[18]
	1.0	1.39	3.7	[20]

GBCA: Gadolinium-based contrast agent.

Table 3.
Physiochemical properties of formulations of gadolinium complexes.

GBCAS	log K (therm)	1/T1 relaxivity $(1/mmol^{-1})s^{-1}$	References
Gd-DTPA	22.2	3.8	[18]
Gd-DTPA-BMA	16.9	3.9	[21]
Gd-DOTA	24.7	3.5	[21]
Gd-HP-DO3A	23.8	3.7	[21]
Gd-DO3A-butrol	21.8	3.6	[18]

Table 4.
Thermodynamic stability constants and relaxivities.

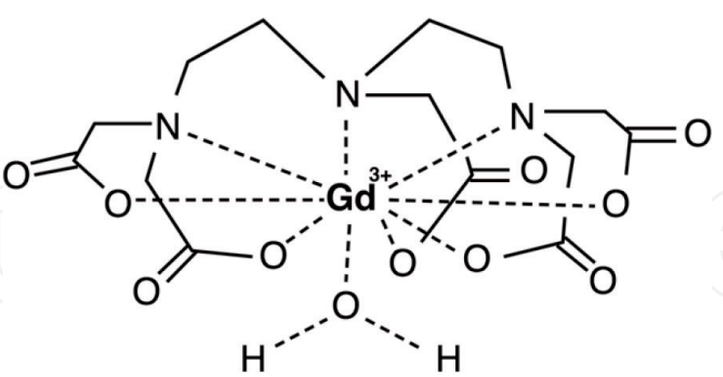

Figure 1.
Gadopentetate dimeglumine, Gd-DTPA (Magnevist).

Gadolinium-DTPA-diamides: Two extracellular contrast agents that contain neutral gadolinium chelates have entered the market: gadodiamide, Gd-DTPA-BMA (Omniscan) (**Figure 2**), and gadoversetamide (Optimark) (**Figure 3**). Both ligands are amides of DTPA and are obtained by treating the dianhydride of DTPA, corresponding to amine. These gadolinium complexes are freely soluble in water. As expected, the osmolality of the 0.5 molar solution of gadodiamide is lower (0.79 osmol/kg water) than that of the 0.5 molar solution of Gd-DTPA.

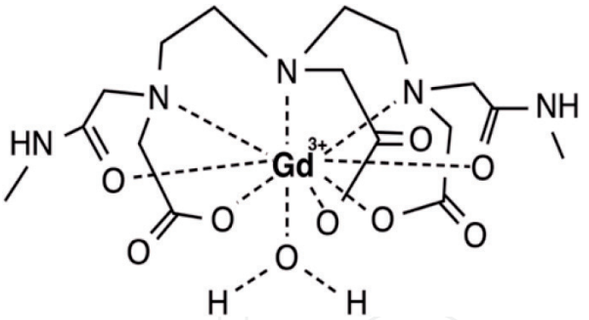

Figure 2.
Gadodiamide, Gd-DTPA-BMA (Omniscan).

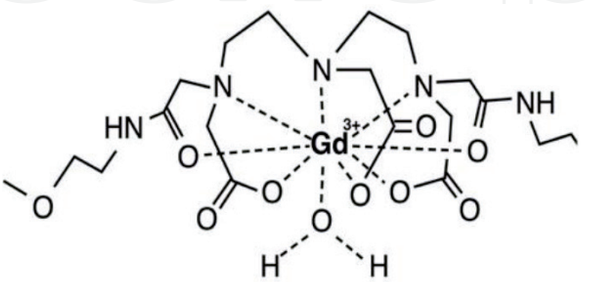

Figure 3.
Gadoversetamide (Optimark).

2.2 Macrocyclic chelates

Gadolinium-DOTA: The second generation of GBCAs contains the derivatives of the macrocyclic tetramine, 1.4.7.10-tetraazacyclododecane (cyclen). Gadoterate, Gd-DOTA (Dotarem, **Figure 4**), was the first macrocyclic gadolinium complex that was released in the market. In the macrocyclic structure, the metal-binding site within the ligand is more encapsulated, and the entropy is decreased upon metal incorporation. According to previous results, the stability of macrocyclic metal chelates is higher than that of linear complexes. The macrocyclic complexes exhibit a higher kinetic stability [10].

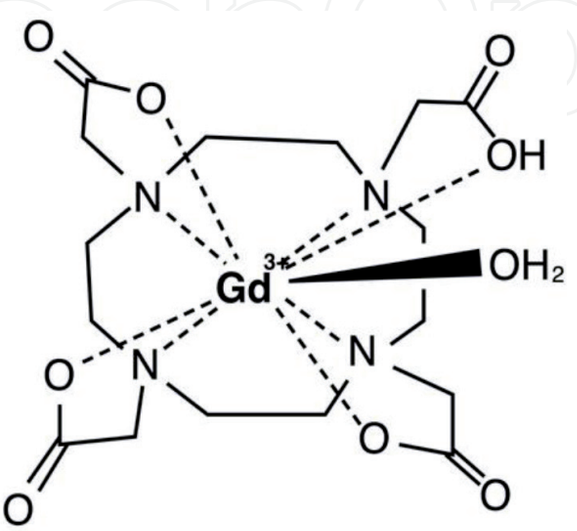

Figure 4.
Gadoterate, Gd-DOTA (Dotarem).

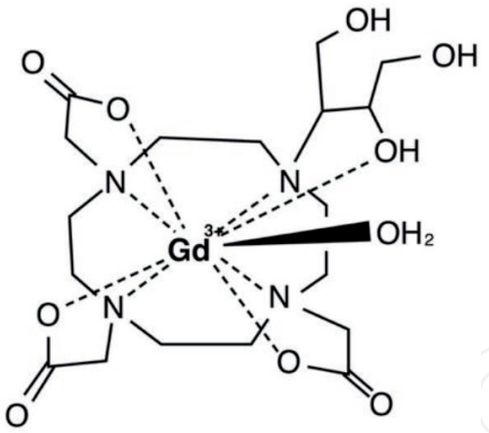

Figure 5.
Gadobutrol (Gadovist).

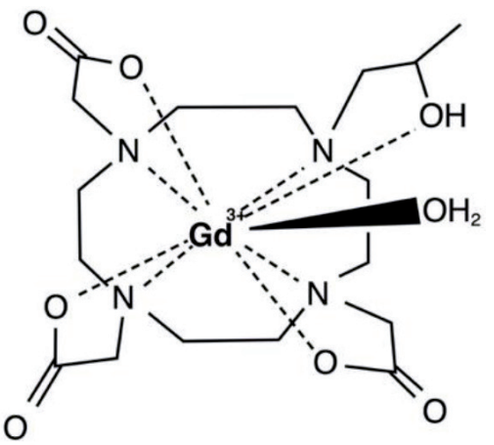

Figure 6.
Gadoteridol (ProHance).

Gadolinium-DO3A: The nonionic open-chain metal chelates and neutral macrocyclic gadolinium chelates have been synthesized. Two of them such as gadobutrol (Gadovist) (**Figure 5**) and gadoteridol (ProHance) (**Figure 6**) have been launched as extracellular MRI contrast agents. Both agents are derivatives of 1,4,7-tricarboxymethyl-1,4,7,10-tetraazacyclododecane (DO3A).

Thermodynamic stability constants and relaxivities in water at 20 MHZ and 40°C of commercially available gadolinium chelates.

3. Nephrogenic systemic fibrosis (NSF)

Nephrogenic systemic fibrosis (NSF) is a multi-systemic fibrosing disease that has been characterized by thickening and tightening of the skin and subcutaneous tissues. NSF also includes fibrosis of the skeletal muscle, lung, liver, testis, or myocardium with possible fatal outcomes.

First described in 1997, NSF was initially known as nephrogenic fibrosing dermopathy because of its classic presentation of symmetric, brawny, or erythematous indurated cutaneous plaques that develop in the setting of renal insufficiency [13, 22, 23]. Grobner's published case reports have found an association of NSF with GBCAs exposure when a meticulous chart review was performed. Currently, over 250 documents reporting NSF cases have been registered by Shawn Cowper of Yale University, which have linked 85% of its cases to gadodiamide (Omniscan) [23–25].

3.1 Pathogenesis of NSF

The exact pathogenesis of NSF is still unclear. However, there are some evidences suggesting that it likely involves the migration of CD34 and procollagen-1 positive, circulating fibrocytes from the blood to the engaged tissue as proposed by Cowper. These fibrocytes likely activate a fibrotic response through cytokine production and T-cell activation. Several reports have shown increased expression of transforming growth factor β1 and CD68-factor XIIIa within the affected skin and skeletal muscle which are also essential markers associated with wound healing and fibrosis [26, 27].

In addition, evidence of in vivo transmetallation has been provided by a preclinical trial in which rats exposed to repeated high-dose GBCAs injection developed an NSF-like skin lesion consisting of epidermal ulceration, acanthosis, dermal fibrosis, and CD34 fibrocytic infiltration with high concentrations of gadolinium in the skin. These findings were more severe with gadodiamide (Omniscan) than gadopentetate (Magnevist) [28]. The differences in conditional thermodynamic stability constants and stimulatory response of gadodiamide on fibroblasts may explain the higher incidence of NSF with gadodiamide (Omniscan). The medical literature report of NSF and this additional evidence seem to indicate a stratified risk within the class of GBCAs. The transmetallation of the gadolinium chelate would occur because of exchange of Gd3+ ions for endogenous metals (such as Zn, Cu, and Ca), and then free Gd3+ ions are released from the chelate. Patients with severe or end-stage renal disease are more likely to undergo in vivo transmetallation because of markedly prolonged clearance of GBCA. This theory has been substantiated by detection of gadolinium within tissue months after GBCA exposure. And transmetallation of Gd-DTPA with endogenous Fe(II)/Fe(III) is possible in human blood plasma. Telgmann concluded that transmetallation may be a trigger of NSF if free Fe(III) ions were accessible during a prolonged pathway of Gd complexes with linear ligands through the patient's body [29].

3.1.1 Clinical features of NSF

1. Onset: A few days to 20 years later. The early clinical symptoms of NSF include pain, pruritus, swelling, erythema (usually starts in the legs), transient alopecia, as well as gastrointestinal symptoms of nausea, vomiting, diarrhea, and abdominal pain.

2. Lately, main symptoms emerge such as nodules developing on the skin; thickened skin and subcutaneous tissues, "woody" texture and brawny plaques; joint regulation; and severe pain. Additionally, the fibrosis process involves the internal organs, e.g., muscle, diaphragm, heart, liver, and lungs. All these processes could lead to joint contractures, cachexia, and death, in a proportion of patients [12, 24].

3.2 Risk patients

High-risk patients have a history of CKD 4 and 5 (glomerular filtration rate (GFR) < 30 ml/min), dialysis, and with reduced renal function who have had or are awaiting liver transplantation. The lower risk includes patients with CKD 3 (GFR 30–59 ml/min) and children under 1 year, because of their immature renal function [22]. Younger children and elderly persons are not affected by NSF because their immune system is immature [23]. Although the pathogenesis is not revealed, the immune system might have a key role in inducing NSF.

No cases of NSF have been reported in patients with GFR greater than 60 ml/min. The role of various possible cofactors in the pathogenesis of NSF is not proven.

Pregnant patients. In the absence of specific information, it seems wise to manage pregnant patients, regardless of their renal function, in the same way as children aged under 1 year to protect the fetus.

In the use of GBCAs, serum creatinine should be measured before gadolinium contrast media administration for all patients.

3.2.1 Key points of risk patients

1. Approximately 40–50% of MRI patients receive Gd-CM.

2. The percentage of patients with CKD 3, 4, and 5 varies in different institutions.

3. Serum creatinine and estimated GFR (eGFR) are not always very accurate indicators of true GFR. In particular, acute renal failure may not be indicated by a single eGFR value.

4. Measurement of serum creatinine/eGFR before Gd-CM is mandatory before Gd-CM which have been associated with subsequent development of NSF.

5. Measurement of serum creatinine/eGFR is not necessary in all patients receiving Gd-CM.

3.3 Use of gadolinium-based contrast agents

Three GBCAs (gadodiamide, gadoversetamide, and gadopentetic acid) are currently FDA-contraindicated in patients with GFR <30 mL/min/1.73 m^2. The American College of Radiology (ACR) recommends screening GFR of any patients with known or suspected renal impairment and advises against the use of any GBCA in patients with GFR <30 mL/min/1.73 m^2, suffering acute kidney injury, or requiring dialysis [30].

3.3.1 General points

1. The risk of inducing NSF must always be weighed against the risk of denying patients gadolinium-enhanced scans which are essential for patient management.

2. In patients with impaired renal function, liver transplant patients, and neonates, the benefits and risks of gadolinium enhancement should be considered particularly carefully.

3. In patients with CKD 4 and 5 (<30 ml/min):

   - Always use the smallest possible amount of the contrast agent to achieve an adequate diagnostic examination.

   - Never use more than 0.3 mmol/kg of any Gd-CM.

   - Never use gadolinium as a contrast agent for radiography, computed tomography, or angiography as a method of avoiding nephropathy associated with iodinated contrast media.

3.4 How to choose gadolinium-based contrast agents?

There are differences in the incidence of NSF with different GBCAs, which appear to be related to differences in physicochemical properties and stability. Since macrocyclic GBCAs are preorganized rigid rings of almost optimal size to cage the gadolinium ions which have high stability compared with linear GBCAs, macrocyclic GBCAs are recommended to inject to patients with mild to moderate CKD. According to the current knowledge about the properties of the different agents and the incidence of NSF, macrocyclic GBCAs should be used for high-risk patients [31].

4. Gadolinium deposition in human body

4.1 Retention of gadolinium

The retention of gadolinium in the human body has become an issue of considerable global interest these days. Gadolinium retention was observed in the bone and in the brain in patients without renal failure [32]. The pharmacokinetics of different gadolinium chelates have been studied in healthy patients and in those with varying degrees of renal impairment. The main pathway of elimination is glomerular filtration [33]. The mean elimination half-life of GBCAs is 1.3–1.5 h. In patients with severe renal insufficiency, the half-life increases to 34.3 h [7]. Currently, it is known that gadolinium is retained in body tissues, regardless of levels of renal function or even GBCA stability [22]. Higher concentrations appear to occur in patients with renal impairment or after exposure to less stable GBCAs [34].

Our recent study found that a long-term Gd retention for GBCAs was almost unaffected by renal function [35, 36]. This finding suggested that the chemical structures of retained Gd may not be homogeneous and some Gd could be slowly eliminated after being initially retained in the tissues. Moreover, Gd retention was greater when linear GBCA was administered, than macrocyclic GBCA. However, the presence of the blood–brain barrier (BBB) likely plays a role in the mechanism of Gd retention in the brain. The mechanism of retention and the shapes of GBCAs have not been adequately revealed yet. Although injection doses should be minimized for all patients, some reports suggest that injection times would be more important than injection doses [27, 37–39].

Gadolinium has some isotopes such as 154Gd, 155Gd, 156Gd, 157Gd, 158Gd, and 160Gd as stable isotopes and 152Gd as a radioisotope. Biodistribution study of various GBCAs was performed in 1995 using a radioisotope of 153Gd. 153Gd was labeled to gadopentetate (Magnevist), gadoteridol (ProHance), gadoterate (Dotarem), and gadodiamide (Omniscan) [40]. All GBCAs were excreted from animal body within 60 min, and GBCAs in blood pool were completely disappeared. The liver, kidney, femur bone, and gastrointestinal tract still retain GBCAs until 14 days. These days the measurements of gadolinium are performed by inductively coupled plasma mass spectroscopy (ICP-MS). In our researches, either 158Gd or 160Gd is measured by ICP-MS. The technology of imaging mass would contribute to reveal the distribution of gadolinium in vivo [41, 42].

Gregory WW reported the gadolinium concentration remaining in human bone tissue after administration of 0.1 mmol/kg of two types of GBCA, Omniscan (Gd-DTPA-BMA) or ProHance (Gd-HP-DO3A), to patients undergoing hip replacement surgery. Tissue retention in bone for Omniscan (Gd-DTPA-BMA) was significantly higher than those for ProHance (Gd-HP-DO3A) measured by ICP-MS. Omniscan (Gd-DTPA-BMA) left approximately four times more

gadolinium behind in bone than did ProHance (Gd-HP-DO3A). These results would indicate two important issues: (1) chelate stability and (2) affinity of GBCA to the bone. Linear GBCAs like Omniscan (Gd-DTPA-BMA) would release more Gd^{3+} ions than macrocyclic GBCAs like ProHance (Gd-HP-DO3A). Since the bone is a known natural repository for unchelated Gd^{3+} ions, free Gd^{3+} ions released from Omniscan (Gd-DTPA-BMA) would retain bone. Another reason to deposit gadolinium to bone would be the affinity of GBCAs to bone. Hydroxyapatite structure is similar to the structure of DTPA. It might be one of causes for linear GBCAs, especially Gd-DTPA or Gd-DTPA-BMA to retain bone.

4.2 Gadolinium deposition in the brain (Kanda reports)

In 2014, Kanda et al. reported unusual brain MRI findings in patients with a history of various GBCAs administration [43] (**Figures 7** and **8**). High signal intensity of the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images was seen in patients with frequent administrations of GBCAs. Signal intensities on T1WI showed a positive correlation with the number of previous GBCA administrations, even in patients with normal renal function. Furthermore, the positive correlation with numbers of GBCA administrations and signal intensities on T1WI was noted only for patients with linear GBCA administrations, while no correlations were seen in patients with macrocyclic GBCA administrations [15, 44, 45]. Several researchers also reported a presence of hyperintensity in the dentate nucleus that corresponded with the number of past linear GBCAs administrations [46, 47]. Similar findings were reported in pediatric patients [30, 43].

The cause of high signals in the globus pallidus continues to be a hot topic in this field. Cadaver studies with quantitative analyses using mass spectroscopy revealed high signal intensities of the globus pallidus in patients with frequent GBCA administrations would be based on gadolinium. Although high signal intensities in the globus pallidus have been also observed in patients who have a history of liver failure, Wilson disease, Osler-Weber-Rendu disease, manganese toxicity, calcification, hemodialysis, total parenteral nutrition, and neurofibromatosis type 1, various kinds of metal ions would be deposited in the globus pallidus. However, the forms of gadolinium deposition have not been known whether chelate type,

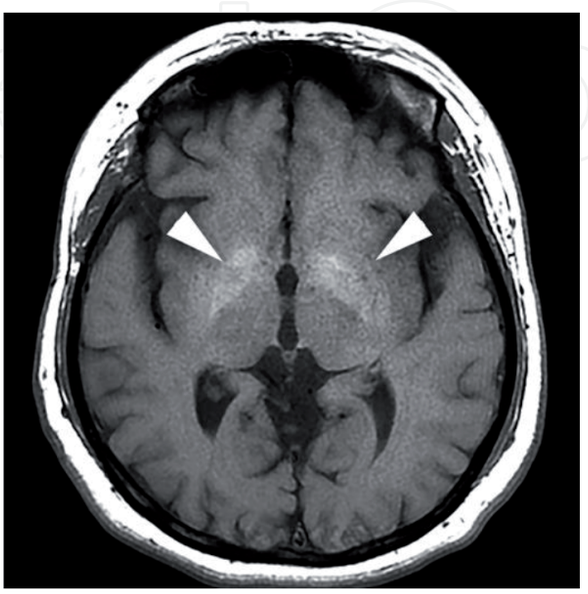

Figure 7.
Unenhanced T1-weighted MR image. Signal increase on unenhanced T1-weighted MR image in the basal ganglia, which is indicated by arrowheads.

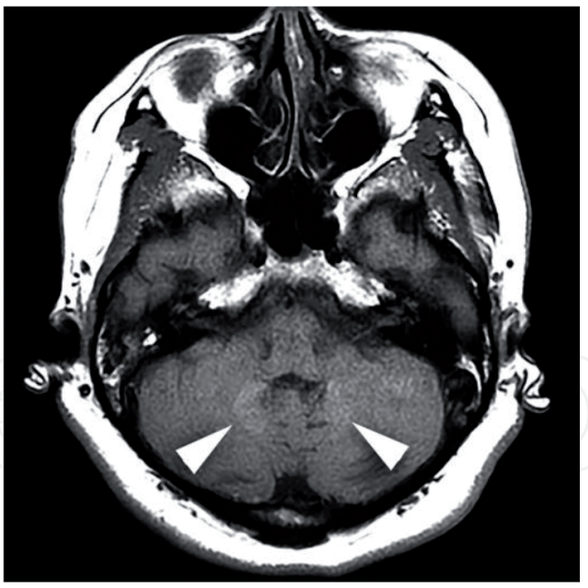

Figure 8.
Unenhanced T1-weighted MR image. Signal increase on unenhanced T1-weighted MR image in the dentate nucleus of the cerebellum, which is indicated by arrowheads.

gadolinium ions, and phosphate or other complexes. In serum or blood, gadolinium ion released from GBCAs tends to bind to phosphate quickly and to make a form of phosphate complex with gadolinium. Since phosphate complex has no signals on MRI, phosphate complex would not be a cause of high signals in the globus pallidus. In our speculation, macromolecules of gadolinium bound to protein would be one of the candidates for deposition in the brain. The reason for our speculation is that gadolinium ions bound to macromolecules show much brighter signals on T1WI than those of small molecules, which is based on the model known as the Solomon-Bloembergen-Morgan formula. Since the macromolecule rotates slowly compared with small molecules, the contact time with gadolinium and water proton can be prolonged, and the T1 shortening effect of gadolinium can be increased. The high signals in the globus pallidus would be derived from the role of macromolecules bound to gadolinium.

4.3 Effect in the central nervous system (CNS)

Gd^{3+} affects the development of infant CNS: In our previous study, we reported that Gd was transferred to pups and was retained in their brain during postnatal period. The perinatal exposure to GBCAs induced behavioral changes in mice; gadodiamide (Omniscan) had a more severe effect than gadoterate meglumine (Dotarem). All pups were separated from mothers for weaning on P21, and the total Gd in the brain of mothers and pups were measured on P28. Higher dose of Gd retention was found in mothers and pups in the linear-type group. Perinatal administration of GBCAs caused anxiety-like behaviors, disrupted motor coordination, impaired memory function, stimulated tactile sensitivity, and decreased muscle strength, especially in the gadodiamide-treated group [48]. In linear GBCA group, the total Gd retention in the brain of the mothers and the pups was higher than in the macrocyclic group. Both GBCAs were intravenously injected with 2 mmol/kg into the mothers from E15 to E19, which is the critical period for the development of neuronal circuits in fetus. According to the results of this study, we investigated Gd retention in various organs in both the mother and pup mice models [49]. Gd retentions in mother mice were consistently higher after gadodiamide (Omniscan) administration than gadoterate meglumine (Dotarem). Moreover, significantly

higher Gd retention was observed in the organs of pups after whose mothers were administered gadodiamide (Omniscan) than gadoterate meglumine (Dotarem) (**Figure 9**). The results indicated that the linear GBCA affected not only the brain but also other maternal organs, such as the bone, spleen, and liver. Though the effects of maternal GBCA administration have not been reported in humans, our studies would warn the potential risk of using GBCAs in pregnant women.

4.4 Glymphatic system

The glymphatic system is discovered as a brain waste system to transport low molecular weight materials from the cerebrospinal fluid (CSF) to the interstitial fluid (ISF). The glymphatic system may also transport GBCAs to the brain. Ilif et al. examined GBCA deposition in the brain with rat by MRI [50]. When GBCA was injected into the rat subarachnoid space, it moved along the basilar artery into the brain parenchyma. In addition, Eide et al. evaluated patients who had GBCA administrations in the subarachnoid space with MRI [51]. Four hours after GBCA administration in the subarachnoid space, both the cortical and white matter of the brain showed high signal intensities, and the gadolinium entrance to the human brain through the glymphatic system was speculated. Naganawa et al. reported that on post contrast FLAIR image, the subarachnoid space and perivascular space showed increased signal intensities and GBCA transfer to the subarachnoid space and perivascular space on brain MRI of 27 subjects who had administrated GBCA before 4 h [52].

These results demonstrated that even in patients with normal renal function, intravenously administered GBCA can be transported through the glymphatic system and reach the brain. However, the association between the hyperintensity in the globus pallidus and dentate nucleus and the GBCA that is transported through the glymphatic system is still unclear. The glymphatic system transports all low molecular weight materials passively, and both the linear type of GBCA and macrocyclic GBCA are transported in the same way. However, the signal intensity of the dentate

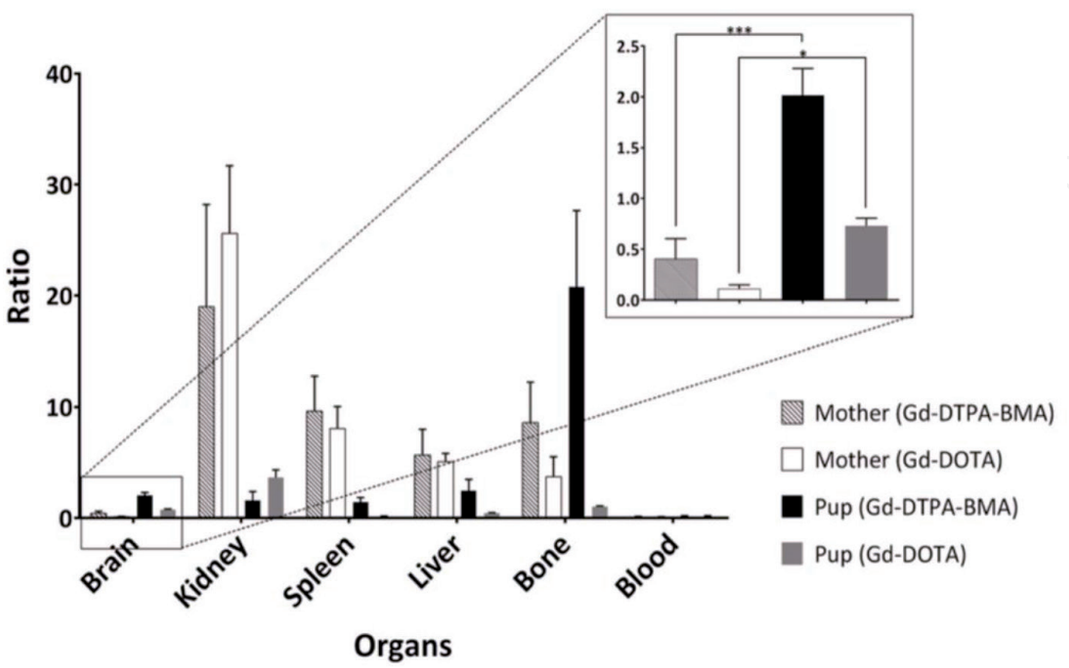

Figure 9.
Gadolinium depositions in organs of mother mice and their pups. The gadolinium concentrations in the organs of mice with the administration of linear GBCA (Gd-DTPA-BMA) were higher than those of macrocyclic GBCA (Gd-DOTA) [49].

nucleus varies according to the type of administered GBCA. In addition, the distribution of gadolinium cannot be explained by passive transportation. The accumulation of GBCA in the brain is probably due to some extent to the glymphatic system, but any association between the glymphatic system and signal hyperintensity of the dentate nucleus remains obscure.

5. Conclusion

We discussed two types of GBCAs: linear chelates and macrocyclic chelates. The macrocyclic GBCAs are more stable than the linear types because free Gd ions do not get released from the macrocyclic chelates easily in various conditions. Many preclinical and clinical studies have revealed higher deposition of Gd in the body organs in linear type than those in macrocyclic GBCAs.

Special precaution needs to be taken in cases of chronic kidney disease or patients with renal dysfunction as the only route of excretion of the GBCAs is via the kidney. Nephrogenic system fibrosis (NSF) has been noted in such renal function-impaired patients who had been administered GBCAs, especially linear types. Moreover, linear GBCAs are easy to release Gd ions from chelates. Linear GBCAs have a tendency to be deposited in the human body, including brain tissue. The use of macrocyclic GBCAs should be recommended even for patients with normal renal function.

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Conflict of interest

The authors have no conflicts of interest directly relevant to the content of this article.

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References

[1] Haacke EM, Brown RW, Thompson MR, Venkatesan R. Magnetic Resonance Imaging: Physical Principles and Sequence Design. Vol. 82. New York: Wiley-Liss; 1999

[2] Zhou Z, Lu Z-R. Gadolinium-based contrast agents for magnetic resonance cancer imaging. Wiley Interdisciplinary Reviews Nanomedicine Nanobiotechnology. 2013;**5**:1-18. DOI: 10.1002/wnan.1198

[3] Morris SA, Slesnick TC. Magnetic resonance imaging. Visual Guide to Neonatal Cardiology. 2018:104-108

[4] Runge VM. Chapter 14. Contrast media BT-clinical MRI. Clinical MRI. 2002:454-472

[5] Kanda T, Nakai Y, Oba H, Toyoda K, Kitajima K, Furui S. Gadolinium deposition in the brain. Magnetic Resonance Imaging. 2016;**34**:1346-1350. DOI: 10.1016/j.mri.2016.08.024

[6] Telgmann L, Sperling M, Karst U. Determination of gadolinium-based MRI contrast agents in biological and environmental samples: A review. Analytica Chimica Acta. 2013;**764**:1-16. DOI: 10.1016/j.aca.2012.12.007

[7] Rai AT, Hogg JP. Persistence of Gadolinium in CSF: A diagnostic pitfall in patients with end-stage renal disease. American Journal of Neuroradiology. 2001;**22**:1357-1361

[8] Nordenskiold L, Laaksonen A, Kowalewski J. Applicability of the Solomon-Bloembergen equation to the study of paramagnetic transition metal-water complexes. An ab initio SCF-MO study. Journal of the American Chemical Society. 1982;**104**:379-382. DOI: 10.1021/ja00366a002

[9] Frenzel T, Lengsfeld P, Schirmer H, Hütter J, Weinmann HJ. Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37 degrees C. Investigative Radiology. 2008;**43**:817-828. DOI: 10.1097/RLI.0b013e3181852171

[10] Caravan P, Ellison JJ, McMurry TJ, Lauffer RB. Gadolinium(III) chelates as MRI contrast agents: Structure, dynamics, and applications. Chemical Reviews. 1999;**99**:2293-2352. DOI: 10.1021/cr980440x

[11] Bellin M. MR contrast agents, the old and the new. European Journal of Radiology. 2006;(3):314-323

[12] Grobner T. Erratum: Gadolinium—A specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? (Nephrology, Dialysis, Transplantation (2006;**21**:1104-1108)). Nephrology, Dialysis, Transplantation. 2006;**21**:1745. DOI: 10.1093/ndt/gfl294

[13] Thomsen HS, Marckmann P, Logager VB. Nephrogenic systemic fibrosis (NSF): A late adverse reaction to some of the gadolinium based contrast agents. Cancer Imaging. 2007;**7**:130-137. DOI: 10.1102/1470-7330.2007.0019

[14] Sethi R, MacKeyev Y, Wilson LJ. The Gadonanotubes revisited: A new frontier in MRI contrast agent design. Inorganica Chimica Acta. 2012;**393**: 165-172. DOI: 10.1016/j.ica.2012.07.004

[15] Runge VM. Macrocyclic versus linear gadolinium chelates. Investigative Radiology. 2015;**50**:811. DOI: 10.1097/RLI.0000000000000229

[16] Tóth É, Helm L, Merbach AE. In: Krause W, editor. Relaxivity of MRI Contrast Agents BT—Contrast Agents I: Magnetic Resonance Imaging. Berlin, Heidelberg: Springer Berlin Heidelberg; 2002. pp. 61-101. DOI: 10.1007/3-540-45733-X_3

[17] Doucet D, Meyer D, Bonnemain B, Doyon D, Caille JM. Gd-DOTA. Enhanced Magnetic Resonance Imaging. St. Louis, MO: Mosby; 1989. pp. 87-104

[18] Vogler H, Platzek J, Schuhmann-Giampieri G, Frenzel T, Weinmann H-J, Radüchel B, et al. Pre-clinical evaluation of gadobutrol: A new, neutral, extracellular contrast agent for magnetic resonance imaging. European Journal of Radiology. 1995;**21**:1-10. DOI: 10.1016/0720-048X(95)00679-K

[19] Tweedle MF. Physicochemical properties of gadoteridol and other magnetic resonance contrast agents. Investigative Radiology. 1992;**27**:S7

[20] Tweedle MF, Hagan JJ, Kumar K, Mantha S, Chang CA. Reaction of gadolinium chelates with endogenously available ions. Magnetic Resonance Imaging. 1991;**9**:409-415

[21] Lauffer RB. Paramagnetic metal complexes as water proton relaxation agents for NMR imaging: Theory and design. Chemical Reviews. 1987;**87**:901-927

[22] Othersen JB, Maize JC, Woolson RF, Budisavljevic MN. Nephrogenic systemic fibrosis after exposure to gadolinium in patients with renal failure. Nephrology, Dialysis, Transplantation. 2007;**22**:3179-3185. DOI: 10.1093/ndt/gfm584

[23] Deo A, Fogel M, Cowper SE. Nephrogenic systemic fibrosis: A population study examining the relationship of disease development to gadolinium exposure. Clinical Journal of the American Society of Nephrology. 2007;**2**:264-267. DOI: 10.2215/CJN.03921106

[24] Broome DR. Nephrogenic systemic fibrosis associated with gadolinium based contrast agents: A summary of the medical literature reporting. European Journal of Radiology. 2008;**66**:230-234. DOI: 10.1016/j.ejrad.2008.02.011

[25] Kanda T, Fukusato T, Matsuda M, Toyoda K, Oba H, Kotoku J, et al. Gadolinium-based contrast agent accumulates in the brain even in subjects without severe renal dysfunction: Evaluation of autopsy brain specimens with inductively coupled plasma mass spectroscopy. Radiology. 2015;**276**:228-232. DOI: 10.1148/radiol.2015142690

[26] Jiménez SA, Artlett CM, Sandorfi N, Derk C, Latinis K, Sawaya H, et al. Dialysis-associated systemic fibrosis (nephrogenic fibrosing dermopathy): Study of inflammatory cells and transforming growth factor β1 expression in affected skin. Arthritis and Rheumatism. 2004;**50**:2660-2666. DOI: 10.1002/art.20362

[27] Lever E, Sheer D. The role of nuclear organization in cancer. The Journal of Pathology. 2010;**220**:114-125. DOI: 10.1002/path

[28] Sieber MA, Pietsch H, Walter J, Haider W, Frenzel T, Weinmann HJ. A preclinical study to investigate the development of nephrogenic systemic fibrosis: A possible role for gadolinium-based contrast media. Investigative Radiology. 2008;**43**:65-75

[29] Telgmann L, Wehe CA, Künnemeyer J, Bülter AC, Sperling M, Karst U. Speciation of Gd-based MRI contrast agents and potential products of transmetalation with iron ions or parenteral iron supplements. Analytical and Bioanalytical Chemistry. 2012;**404**:2133-2141. DOI: 10.1007/s00216-012-6404-x

[30] Gale EM, Caravan P, Rao AG, McDonald RJ, Winfeld M, Fleck RJ, et al. Gadolinium-based contrast agents in pediatric magnetic resonance imaging. Pediatric Radiology. 2017;**47**:507-521. DOI: 10.1007/s00247-017-3806-0

[31] Thomsen HS. ESUR guideline: Gadolinium-based contrast media and

nephrogenic systemic fibrosis. European Radiology. 2007;**17**:2692-2696. DOI: 10.1007/s00330-007-0744-5

[32] High WA, Ayers RA, Chandler J, Zito G, Cowper SE. Gadolinium is detectable within the tissue of patients with nephrogenic systemic fibrosis. Journal of the American Academy of Dermatology. 2007;**56**:21-26. DOI: 10.1016/j.jaad.2006.10.047

[33] Staks T, Schuhmann-Giampieri G, Frenzel T, Weinmann HJ, Lange L, Platzek J. Pharmacokinetics, dose proportionality, and tolerability of gadobutrol after single intravenous injection in healthy volunteers. Investigative Radiology. 1994;**29**:709-715

[34] Ramalho J, Ramalho M, Jay M, Burke LM, Semelka RC. Gadolinium toxicity and treatment. Magnetic Resonance Imaging. 2016;**34**:1394-1398. DOI: 10.1016/j.mri.2016.09.005

[35] Kartamihardja AAP, Nakajima T, Kameo S, Koyama H, Tsushima Y. Impact of impaired renal function on gadolinium retention after administration of gadolinium-based contrast agents in a mouse model. Investigative Radiology. 2016;**51**:655-660. DOI: 10.1097/RLI.0000000000000295

[36] Kartamihardja AAP, Nakajima T, Kameo S, Koyama H, Tsushima Y. Distribution and clearance of retained gadolinium in the brain: Differences between linear and macrocyclic gadolinium based contrast agents in a mouse model. The British Journal of Radiology. 2016;**89**. DOI: 10.1259/bjr.20160509

[37] 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 & Development. 2016;**38**:331-336. DOI: 10.1016/j.braindev.2015.08.009

[38] Africa S. HHS Public Access. 2017;**4**:237-241. DOI: 10.1016/S2214-109X(16)30265-0.Cost-effectiveness

[39] Radbruch A, Weberling LD, Kieslich PJ, Eidel O, Burth S, Kickingereder P, et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. Radiology. 2015;**275**:783-791. DOI: 10.1148/radiol.2015150337

[40] Tweedle MF, Wedeking P, Kumar K. Biodistribution of radiolabeled, formulated gadopentetate, gadoteridol, gadoterate, and gadodiamide in mice and rats. Investigative Radiology. 1995;**30**:372-380

[41] Aichler M, Huber K, Schilling F, Lohöfer F, Kosanke K, Meier R, et al. Spatially resolved quantification of gadolinium(III)-based magnetic resonance agents in tissue by MALDI imaging mass spectrometry after in vivo MRI. Angewandte Chemie—International Edition. 2015;**54**:4279-4283. DOI: 10.1002/anie.201410555

[42] White GW, Gibby WA, Tweedle MF. Comparison of Gd (DTPA-BMA) (Omniscan) versus retention in human bone tissue by inductively coupled plasma mass spectroscopy. Investigative Radiology. 2006;**41**:272-278. DOI: 10.1097/01.rli.0000186569.32408.95

[43] Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images. Radiology. 2014;**270**:1-6

[44] Gulani V, Calamante F, Shellock FG, Kanal E, Reeder SB. Gadolinium deposition in the brain: Summary of evidence and recommendations. Lancet Neurology. 2017;**16**:564-570. DOI: 10.1016/S1474-4422(17)30158-8

[45] Radbruch A, Weberling LD, Kieslich PJ, Hepp J, Kickingereder P, Wick W, et al. High-signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted images: Evaluation of the macrocyclic gadolinium-based contrast agent gadobutrol. Investigative Radiology. 2015;**50**:805-810. DOI: 10.1097/RLI.0000000000000227

[46] McDonald RJ, McDonald JS, Kallmes DF, Jentoft ME, Murray DL, Thielen KR, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology. 2015;**275**:772-782. DOI: 10.1148/radiol.15150025

[47] Errante Y, Cirimele V, Mallio CA, Di Lazzaro V, Zobel BB, Quattrocchi CC. Ovid 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. Investigative Radiology. 2014;**49**:685-690

[48] Khairinisa MA, Takatsuru Y, Amano I, Erdene K, Nakajima T, Kameo S, et al. The effect of perinatal gadolinium-based contrast agents on adult mice behavior. Investigative Radiology. 2018;**53**:110-118. DOI: 10.1097/RLI.0000000000000417

[49] Erdene K, Nakajima T, Kameo S, Khairinisa MA, Lamid-Ochir O, Tumenjargal A, et al. Organ retention of gadolinium in mother and pup mice: Effect of pregnancy and type of gadolinium-based contrast agents. Japanese Journal of Radiology. 2017;**35**:568-573. DOI: 10.1007/s11604-017-0667-2

[50] Iliff JJ, Lee H, Yu M, Feng T, Logan J, Nedergaard M, et al. Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. The Journal of Clinical Investigation. 2013;**123**:1299-1309. DOI: 10.1172/JCI67677

[51] Eide PK, Ringstad G. MRI with intrathecal MRI gadolinium contrast medium administration: A possible method to assess glymphatic function in human brain. Acta Radiologica Short Reports. 2015;**4**:205846011560963. DOI: 10.1177/2058460115609635

[52] Naganawa S, Nakane T, Kawai H, Taoka T. Gd-based contrast enhancement of the perivascular spaces in the basal ganglia. Magnetic Resonance in Medical Sciences. 2017;**16**:61-65. DOI: 10.2463/mrms.mp.2016-0039