Gadolinium Retention and Toxicity—An Update

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Until 2006, the main considerations regarding safety for all gadolinium-based contrast agents (GBCAs) were related to short-term adverse reactions. However, the administration of certain "high-risk" GBCAs to patients with renal failure resulted in multiple reported cases of nephrogenic systemic fibrosis. Findings have been reported regarding gadolinium deposition within the body and various reports of patients who report suffering from acute and chronic symptoms secondary to GBCA's exposure. At the present state of knowledge, it has been proved that gadolinium deposits also occur in the brain, irrespective of renal function and GBCAs stability class. To date, no definitive clinical findings are associated with gadolinium deposition in brain tissue. Gadolinium deposition disease is a newly described and probably infrequent entity. Patients presenting with gadolinium deposition disease may show signs and symptoms that somewhat follows a pattern similar but not identical, and also less severe, to those observed in nephrogenic systemic fibrosis. In this review, we will address gadolinium toxicity focusing on these 2 recently described concerns.

Key Words: Gadolinium-based contrast agents, Gadolinium storage condition, Gadolinium deposition disease, Toxicity

INTRODUCTION

Magnetic resonance imaging (MRI) is a powerful, radiation-free tool for clinical diagnosis. The introduction of gadolinium-based contrast agents (GBCAs) in 1988[1] have transformed MRI practice up to the present day. GBCAs affect the intrinsic tissue magnetization behavior characteristics because of T1-relaxivity shortening properties, resulting in increased signal or enhancement that is used for characterization of a variety of benign and malignant disease processes.

Approximately 400 million doses of GBCAs have been administered worldwide. They are considered extremely safe when used in appropriate clinical doses; however, as any other drugs used in clinical practice, GBCAs may also have adverse events and potential risks. GBCAs have an incidence of allergic-like reactions ranging from 0.004% to 0.7%[2] and severe life-threatening anaphylactic reactions ranging from 0.001% to 0.01%.[2-5] Most reactions are mild, physiological in nature, and self-limited. Severe anaphylactic reactions resulting in death are extremely rare and have been reported in approximately 1 in 300,000 administrations of GBCAs with 40 deaths per 51 million administered GBCA doses between 2004 and 2009.[6,7]

Until 2006, the main considerations regarding safety for all GBCA were related to short-term adverse reactions. However, the administration of certain "high-risk" GBCAs to patients with renal failure resulted in multiple reported cases of nephrogenic systemic fibrosis (NSF). NSF was first recognized in 1997 in 15 dialyzed patients and fully described 3 years later by Cowper and colleagues.[8] At that time, it was referred to as nephrogenic fibrosing dermopathy. Its association with GBCA's administration was only established 5 years later.[9,10] To date, NSF still represents the only well-established clinical entity related to toxic effects of gadolinium. The 2 essential prerequisites for this condition have been considered severe renal failure and administration of a GBCA with lower chemical stability.[11] Corroborating this observation, switching from the less stable GBCAs to the more stable ones and restrictions on administration of high-risk GBCAs to patients with renal insufficiency has greatly reduced the incidence of NSF with no new cases reported since 2009.[12]

Before the widespread concern was better elucidated on NSF and long-term gadolinium safety, findings had been reported regarding gadolinium deposition within the body after the use of GBCAs. There is currently a growing global awareness regarding the risks associated with GBCAs, mainly triggered by recent published data regarding gadolinium deposition in brain tissue in patients with normal renal function. Nevertheless, evidence of *in vivo* gadolinium deposition has been reported for at least 1 decade, in particular in bone.[13-15] The Food and Drug Administration drug safety communications statement expressed that no adverse health effects have been identified with repeated use of GBCAs for MRI.[16] However, the European Medicine Agency (EMA) Pharmacovigilance and Risk Assessment Committee has recommended the suspension of the marketing authorizations for four linear gadolinium contrast agents because of evidence that small amounts of the gadolinium they contain are deposited in the brain.[17] The American College of Radiology,[2] and the European Society of Urogenital Radiology[18] have not yet proposed guidelines concerning gadolinium deposition.[19] For gadolinium retention in tissues not associated with any clinical symptomatology, the designation gadolinium storage condition (GSC) was proposed.

Over the past few years, groups of patients who report suffering from acute and chronic symptoms secondary to

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GBCAs exposure have formed gadolinium-toxicity online support groups. Most of these patients had normal renal function, and presumably because of this circumstance, they have been dissuaded by their health care providers from thinking that what they were experiencing was related to gadolinium toxicity. Furthermore, different physicians from different specialties follow patients with normal renal function who undergo MRI with GBCA administration. Therefore, the likelihood that any one-physician group would see a cluster of individuals with this peculiar and distinctive set of findings is extremely low. Considering this and the likelihood of adverse reactions, even if rare, our group initiated investigations on this subject. Our preliminary investigations[20-22] have convinced us that this phenomenon is a true disease process, which we propose naming "gadolinium deposition disease" (GDD).

In this review, we will address gadolinium toxicity focusing on these 2 recently described entities, GSC and GDD.

GADOLINIUM STORAGE CONDITION

Based on their chemical structure and its stability *in vivo*, as measured in human serum stability studies, GBCAs can be classified into 3 groups: nonionic linear, ionic linear, and macrocyclic. Macrocyclic chelates are more stable than linear chelates and ionic linear chelates are more stable than nonionic linear chelates.[23]

Retention of gadolinium in patients with normal renal function has been reported to represent less than 5% of the administered dose.[24] At a standard dose of 0.1 mmol/kg, this translates into a total of 11 to 55 mg of gadolinium if 1% to 5% of a given dose is retained, and this amount can be much higher if a patient receives multiple doses over their lifetime.[25] These findings have stimulated investigations into the re-evaluation of biodistribution of GBCAs and how this may influence or even determine patient care.

Despite the lack of clinical findings, evidence of *in vivo* gadolinium deposition in bone in patients with normal renal function has long been recognized.[13-15] Recently, gadolinium was also found in the brain, independent of renal function, and in the presence of an intact blood–brain barrier. The underlying cause of gadolinium retention remains unclear as well as the long-term and cumulative effects of retained gadolinium in the brain and elsewhere in the body. To our knowledge, no published reports have demonstrated clinical symptoms associated with simple intracranial gadolinium deposition. One recent large study did not find that patients with multiple GBCA-enhanced studies developed a greater incidence of Parkinson's disease than subjects who had not undergone GBCA-enhanced MRI.[26]

Brain Tissue Gadolinium Deposition

Brain gadolinium deposition was first suggested by Kanda and colleagues[27] in 2014 in a study where the authors reported the association of increased signal intensity in the dentate nucleus (DN) and globus pallidus (GP) on unenhanced T1-weighted images in patients with a history of GBCA administration. After Kanda's work, several retrospective MRI observational in vivo studies in humans demonstrated similar signal changes after multiple doses of different GBCAs.[28-35] These studies were followed by postmortem human[36-38] and animal studies, which confirmed the presence of gadolinium in the brain after multiple administrations of GBCAs and also confirmed that the MRI changes were directly related with the intracranial gadolinium retention.[36]

The most current studies have found gadolinium deposits in all evaluated brain tissues, including cerebellar white matter, frontal lobe cortex, frontal lobe white matter, thalami, and pons, and not just the DN and GP, although higher concentration was observed in DN followed by GP. One conclusion was that MRI has a relatively limited sensitivity to detect gadolinium deposition in brain tissue. Despite this limitation, MRI became the best available tool to exhibit gadolinium deposition in brain tissue. The amount of gadolinium deposition in brain has also been shown to correlate with the higher deposition in bone.[38] MRI quantitative analysis may overcome this limitation of detection, as postulated by Kuno and colleagues,[39] who reported on global and regional quantitative assessments of T1 and T2 in brain tissue. An association with previous GBCA exposure for gray matter structures was exhibited, suggesting that with their approach, the wider distribution of gadolinium retention throughout the brain could be shown.[39]

Recent studies in children parallel the reported findings in adults, demonstrating gadolinium deposition in the brain[40-43] with repeated exposure to GBCAs. Further studies with larger patient cohorts, different GBCAs, and postmortem pathologic analysis are needed to confirm pediatric intracranial gadolinium deposition and determine its clinical significance, especially within the vulnerable pediatric population. It should be recognized that these patients might potentially have repeated gadolinium exposure over their lifetime. Clinicians and radiologists should proceed with caution and administer

CLINICAL SUMMARY

- At the present state of knowledge, it has been proved that gadolinium deposits occur in the brain, irrespective of renal function and gadolinium-based contrast agents (GBCAs) stability class, but the amount of retention relates to the stability of the GBCAs, with less stable agents depositing more gadolinium.
- The glymphatic system is a newly described paravascular pathway for cerebrospinal fluid-interstitial fluid exchange in the brain and accumulation of GBCAs in the brain is probably related to some extent to it.
- To date, no definitive clinical findings are associated with gadolinium retention in brain tissue.
- Gadolinium deposition disease is a newly describe and probably infrequent entity that represents a constellation of signs and symptoms in patients with normal renal function who have received a GBCA agent.