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Gadolinium toxicity and treatment

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ABSTRACT

Gadolinium based contrast agents (GBCAs) play an important role in the diagnostic evaluation of many patients. The safety of these agents has been once again questioned after gadolinium deposits were observed and measured in brain and bone of patients with normal renal function. This retention of gadolinium in the human body has been termed "gadolinium storage condition". The long-term and cumulative effects of retained gadolinium in the brain and elsewhere are not as yet understood. Recently, patients who report that they suffer from chronic symptoms secondary to gadolinium exposure and retention created gadolinium-toxicity on-line support groups. Their self-reported symptoms have recently been published. Bone and joint complaints, and skin changes were two of the most common complaints. This condition has been termed "gadolinium deposition disease". In this review we will address gadolinium toxicity disorders, from acute adverse reactions to GBCAs to gadolinium deposition disease, with special emphasis on the latter, as it is the most recently described and least known.

1. Introduction

Gadolinium-enhanced MRI impacts diagnosis and treatment strategies by detecting a wide variety of pathologic processes that would otherwise be undetectable with unenhanced MRI or other imaging modalities. Gadolinium based contrast agents (GBCAs) have been in clinical use for almost 30 years, with more than 300 million doses administered worldwide [1,2]. The general safety profile of these agents has been exceptional; apart from acute adverse events, the great majority of which are mild, and nephrogenic systemic fibrosis (NSF), a rare life-threatening condition seen in patients with severe renal failure, few gadolinium-related toxicities have been reported. A number of conditions may influence gadolinium toxicity, and renal function and molecular structure of the GBCA are the most well known.

GBCAs can be classified according to their biochemical structure as linear or macrocyclic and further subdivided according to their charge as ionic or non-ionic. Macrocyclic chelates are more stable than linear chelates, and ionic linear is more stable than the nonionic linear ones [3]. Stability is the ability of the ligand to retain the Gd^{3+} ion within the complex. Since free gadolinium (Gd^{3+}) is toxic, stability is a critical factor in gadolinium toxicity.

Most GBCAs in clinical use are nonspecific extracellular contrast agents, which, similarly to iodine-based contrast agents, are cleared almost exclusively by the kidneys. Patients with renal impairment have reduced GBCA elimination, and the gadolinium complex remains inside the body for extended periods, allowing dissociation to occur [3,4]. Renal function has been considered a critical determinant of subacute gadolinium toxicity, which became recognized by the radiology community when the association between NSF and GBCA exposure was documented.

In a similar time frame to the recognition of the relationship between gadolinium and NSF, reports were published describing the presence of gadolinium in bone in patients with normal kidney function undergoing hip replacement [5,6]. The potential implication of this was not fully appreciated, until almost a decade later when gadolinium was found in brain tissue [7–9].

In this review we will describe the spectrum of reported gadolinium adverse effects and toxicity.

2. Acute adverse events

When used at clinically approved doses (0.1 to 0.2 mmol/kg for most agents) GBCAs have a long-standing and excellent cumulative safety profile and are extremely well tolerated by the vast majority of patients. The overall adverse event rate ranges between 0.07% and 2.4% [10–12]. Acute adverse events (AE) can be divided according to its mechanism into immediate hypersensitivity (allergic-like) reactions

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(typically occur within seconds or minutes after the injection and imply an immune response to the whole or part of the GBCA) or physiologic reactions (coldness, warmth, or pain at the injection site, nausea with or without vomiting, headache, paresthesias, and dizziness). According to severity, AE can be classified into mild (self-limited with signs and symptoms showing no evidence of progression), moderate (more pronounced symptoms, such as bronchospasm, laryngeal edema, and/or generalized erythema) or severe (life threatening, including severe laryngeal edema, convulsions, profound hypotension, unresponsiveness, arrhythmia, and/or cardiopulmonary arrest) [13].

Most reactions are mild and physiologic in nature. Allergic-like reactions are uncommon and vary in frequency from 0.004% to 0.7% [13]; lower than the rate of incidence for acute adverse reactions associated with low-osmolar nonionic iodinated contrast media used for CT scans, which itself is already low (0.2%) [14].

Severe life-threatening anaphylactic and fatal reactions do occur, but are exceedingly rare (0.001% to 0.01%) [13,15–17], with only 40 deaths reported in 51 million GBCA doses administered between 2004 and 2009 [18]. The rarity of severe reactions makes it difficult to analyze accurately any differences between the reactions associated with individual GBCAs.

Patients with asthma and various other allergies may have a mild increased risk for an allergic-like reaction to GBCAs compared to the general population, but many institutions do not have special procedures for these patients given the extremely low overall reaction rate for these agents [10]. Jung et al. [14] also identified female gender and the number of exposures to MR contrast media as risk factors. Previous allergic reaction to a GBCA [14,18] is also a risk factor. The recurrence rate of hypersensitivity-like reactions is nearly 30% [14]. Indeed, if a patient has a history of reaction to a particular GBCA and further MRI exams are needed, it is recommended to change to a different GBCA, and appropriate premedication with antihistamine and systemic corticosteroid should be considered according to the severity of the previous hypersensitivity reactions [14].

At present there is no evidence to suggest that there is any difference in the incidence of acute adverse events between individual contrast agents. The most appropriate sources for information on acute adverse events are published phase 3 trial results, and phase 4 studies that do not have a commercial association.

3. Nephrogenic systemic fibrosis (NSF)

NSF was linked with GBCAs' exposure in patients with renal insufficiency in 2006 [19,20]. It is a debilitating and potentially life-threatening disease characterized by widespread progressive tissue fibrosis. Currently, it is widely accepted that the two essential underlying factors for NSF are renal failure and GBCA administration, but the exact underlying mechanism is not fully elucidated. NSF has been almost completely eliminated since the mid-2009 by screening patients for the presence of renal disease, by performing unenhanced studies or half-dose GBCA studies in patients at high risk, and changing the agents used avoiding high-risk GBCAs in patients with substantial renal disease. The changes in practice patterns that have led to successful prevention of NSF have been crucial in reassuring the public and health care professionals, and had resulted in a decrease in anxiety associated with use of these contrast agents, until 2014, when gadolinium deposition in brain tissue was noticed.

4. Gadolinium toxicity: reported cases of miscellaneous toxicity

4.1. Non-neurological

Individual case reports have described a variety of toxic occurrences from GBCAs [21]. An acute nephrotoxic effect was reported in a 56-year-old woman with normal baseline renal function who had 2 consecutive vascular imaging procedures employing GBCA administration and a few days later after the second study the patient developed acute renal failure. A renal biopsy revealed acute tubular necrosis Akgun et al. [22]. Another report described recurrent acute pancreatitis in a 58-year-old woman following gadobenate dimeglumine (MultiHance®) administration [23]. Pancreatitis ensued approximately 3 h after initial GBCA exposure and recurred upon subsequent administrations. In another case report, a previously asymptomatic 45-year old woman experienced upper abdominal pain and vomiting 4 h after cranial MRI with gadodiamide (Omniscan®), twelve hours after the onset of her abdominal symptoms, an MRI was performed that revealed severe necrotizing pancreatitis requiring surgical intervention [24].

Gathings et al. [25] recently described histologic features similar to NSF in two patients with normal renal function after receiving gadodiamide (Omniscan®). The authors named it as gadolinium-associated plaques. These plaques (sclerotic bodies) had initially been thought to be pathognomonic for NSF, but in the report by Gathings et al. both patients had no NSF and only one had renal disease [25]. The patient who did not have renal disease received high doses of gadolinium, suggesting that similar histologic features may be present in patients without NSF. This may represent part of the spectrum of GDD.

4.2. Neurological

Gadolinium neurotoxicity was described in two case reports of presumed gadolinium induced encephalopathy, by Maramattom et al. [26] and Hui et al. [27]. In the first case a 57-year-old woman with end stage renal failure developed encephalopathy after repeated intravenous gadolinium-enhanced MR imaging, while the serum free gadolinium level was 28,591 ng/mL (50,000 nmol/mL). Improvement in mental status coincided with the clearance of serum gadolinium and resolution of CSF hyperintensity. In the second case the patient's mass spectrometry detected 23,000 nmol/mL of gadolinium in a CSF sample.

Miller et al. [28] recently described the MRI changes occurring in the brain of a male patient who received 35 GBCA doses of a linear agent (gadopentetate dimeglumine) when he was between the ages of 8 and 20 years. This individual was diagnosed at age 5 years with a rhabdomyosarcoma of the left orbit, underwent surgery, chemotherapy, and external beam radiation and subsequent MR surveillance. At 7 years of age he underwent the first of 35 contrast-enhanced MRI brain examinations. His medical history is notable for several intercurrences. However at 21 years old, he had no intracranial lesion on MRI, significant visible treatment-related intracranial structural abnormality, or significant documented medical problem. No skin lesions were apparent, and renal and hepatobiliary function testing was always normal. Recent neuropsychological testing, suggested difficulties with executive functioning (e.g., planning, working memory, organization, and cognitive flexibility), visual memory and reasoning, reading comprehension, and math abilities. Despite the gadolinium accumulation in the basal ganglia, definite conclusions could not be drawn regarding the cognitive delay and gadolinium due to the considerable brain external beam radiation and proton beam therapy.

5. Gadolinium storage condition

The storage state of gadolinium in the body [29] has received considerable international interest and multiple publications. Gadolinium presence was originally observed in bone [5,6,30] and more recently in the brain [7–9,31–39] in patients with normal renal function.

A recent study looked at gadolinium content in autopsy evaluation of tissue from patients who had had normal kidney function when gadolinium was administered to them. The authors found proportionate content of brain and bone, with bone having approximately 20 times the concentration of gadolinium compared to brain, with both linear and macrocyclic agents [9]. What is currently known, is that gadolinium is retained in body tissues, regardless of renal function or even GBCA stability [5–9]. Higher concentrations appear to occur in patients with renal impairment [40] or after exposure to the less stable GBCAs [41,42]. This entity of simple retention in tissues has been recently termed "gadolinium storage condition (GSC)" [29]. Early reports of gadolinium accumulation in the brain and bone of patients with normal renal function who have undergone multiple gadolinium contrast administrations were initially described in adults. Recent studies in children emulate the reported findings in adults, reflecting gadolinium deposition in the brain [28,43,44]. Whether the accumulated gadolinium is dechelated and associated with different molecules, or chelated in its original formulation is not completely clear.

In a recently published meta-analysis, Lancelot [45] reviewed the data on radiolabelled studies showing the presence of a deep compartment for gadolinium storage in the body. He showed that the toxicokinetic profile of different GBCAs varied according to their chemical structure. In this regard, he showed that gadoterate meglumine (Dotarem®), a macrocyclic GBCA, had a much faster blood clearance than linear GBCAs, which appears to be related to different thermodynamic stability of these agents. Radiolabelled investigation showed that the ligand of gadodiamide (Omniscan®) underwent γ (residual excretion phase) elimination at the same fast rate as the entire chelate of Dotarem®, while the gadolinium atom showed much more prolonged γ rate, suggesting that the chelate had disassociated and the gadolinium was retained in the body. Gadolinium chelate dissociation occurs in vivo, a mechanism that may explain their long-lasting retention and slow release from bone. This seems to show that dechelated gadolinium, especially in the setting of linear agent use, tend to persist in tissue stores and bound to host chemicals, while the ligand is eliminated in the urine.

6. Gadolinium deposition disease

6.1. Definition

Gadolinium deposition disease (GDD) represents symptoms in patients with normal renal function who have received a GBCA agent. The main difference between GSC and GDD is that in GSC gadolinium is presumably inert in the tissues, while in GDD the presence of gadolinium generates considerable symptomatology. In order for GDD to occur, our opinion is that the host generates an immunologic response that is host-destructive, and furthermore we believe that it is dependent on the genetic susceptibility of each individual. There are thus two components that we consider to be essential in GDD: 1) the presence of gadolinium in the body, and 2) the host response to its presence. The recognition of both of these components will become essential, as appropriate therapy will most likely involve addressing both.

A recent survey publication [46] described the most common symptoms of presumed GDD. In a follow-up survey, these authors addressed more specifically symptoms described by patients. Not surprisingly many of these symptoms were analogous to NSF, but less severe. The principal symptoms included: bone pain (peripheral but also central), skin and subcutaneous tissue burning pain (peripheral arm and leg [glove and sock] but also central), and in late stage disease (>3 months) progressive thickening and discoloration of the skin and subcutaneous tissue of the distal arms and legs occurs. Apparently distinct from NSF is the feature of disoriented mentation (patients often term "brain fog") that is frequently described by sufferers, which can be disabling to the point that the person may be unable to continue their normal employment. At the present time it is unclear whether "brain fog" may also be seen in NSF, but is has been described with toxicity of other heavy metals, such as lead.

6.2. Pathophysiology

The onset of GDD seems to arise earlier than with NSF, typically within hours to days of GBCA administration, rather than weeks to months. Our present hypothesis to explain the earlier onset of this condition, is that this disease may be a blend of an acute adverse event, that is a polypeptide-mediated response, with a subacute adverse event, that is cell-mediated.

The acute response component may reflect release of cytokines and chemokines, as has been described in a study by Wermuth et al. [47], in which the authors found that all GBCAs induced specific cytokine and chemokine elaboration. This likely explains why apparently a greater range of GBCAs (including macrocyclic agents) cause GDD, unlike both NSF or GSC which are more strongly related to weaker chelates. In this fashion GDD shares similarities with GBCA-induced acute adverse reactions, and the contribution of acute immune effects may explain why this condition may also be observed even with more stable agents. As with allergic reactions of other types, the reaction can occur both after the first event, but also at a later time following multiple previous administrations, which had not previously caused a reaction. GDD has been described after a single administration of GBCA, but also following multiple prior GBCA administrations, where no reaction had occurred with the early administrations.

The subacute immunologic response is probably analogous to NSF mechanism that has been described as mediated by CD 34+ fibrocytes, which congregate in the subcutaneous tissues in the peripheral arms and legs. We expect that a similar cell-based immunologic response must also be occurring in the late stage of GDD, although not yet histologically proven. It is likely that these CD 34+ fibrocytes are part of the myeloid cell family of immune-responder cells.

Disease processes based on accumulation of material are not rare. One disease that may bear a lot of similarity to GSC vs. GDD and gadolinium presence, is liver disease related to fat accumulation: non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). As with GSC and GDD the difference between the two is based on the interplay of host genetics and immunology, to the presence of fat in the liver. NASH is associated with defined genes, which is not associated with NAFLD [48,49].

Our opinion is that in GDD there may be a genetic abnormality in metabolizing heavy metals. Genetic variability may explain the low incidence of GDD in comparison with the number of patients exposed to GBCAs, and also the variable severity of the symptoms.

In an analogous fashion, a recent paper described inter-individual variability and genetic influences on cytokine responses, but in this report to bacteria and fungi [50]. They reported that there is considerable variability between individuals on the extent of cytokine release to such pathogens, from negligible to complete host-destruction, which is similar to the variability of the severity of disease reported by patients with GDD. The authors of this research also found that the variable immune response is apparently gene-mediated.

6.3. Epidemiology

Discussion had by an author in this review with many of the sufferers in the MRI-gadolinium-toxicity support group and

Gadolinium Toxicity Facebook page, and from our current investigation, suggests that the great majority of these individuals are European-origin white, and many are female. This may represent a selection bias, as these are volunteers from on-line advocacy groups. These patients appear well educated, have access to information on the Internet, and have motivation and intellectual curiosity sufficient to look for a reason for their symptoms; and this stereotype may influence our current thinking on epidemiology. However, our opinion is that it may represent a genetic susceptibility. As it appears to be a condition of difficulty with metal metabolism, the condition is reminiscent of another disease of metal handling, genetic hemochromatosis, which is a gene-based disease that occurs in white individuals of Celtic origin. It may be that difficulty with processing and/or metabolizing metals, or over-reaction to them, may be primarily a European-origin Caucasian person's disease. As further indirect proof of GDD being a predominantly white person's genetic disease, the initial and subsequent publication of gadolinium retained in the dentate nucleus and globus pallidus was made by Kanda et al. [31] on a Japanese population, hence simple storage is likely a universal phenomenon of gadolinium exposure, and especially of linear agents [33,34,36–39]. Yet there are no major series of NSF coming from Japan, South Korea or China [51,52]. Underdiagnosis of NSF is unlikely to explain the numerical discrepancy of NSF incidence in Asian countries compared [52]. Furthermore, although the authors are aware of many cases in North America, and individuals in Australia and Europe complaining of symptoms of GDD, we are unaware of any reports at the present time from Asian countries.

The incidence of GDD and GSC are at present difficult to predict. Regarding GSC it is likely that all individuals who have received 5 or greater MRI studies with a GBCA will have tissue retention of gadolinium, however it seems that the amount of deposited gadolinium depends on the stability of the applied GBCA, being less with macrocyclic agents. Our best guess is that this may number in the millions of individuals. In the great majority of these individuals the gadolinium appears to be inert. Communication with patient activist groups suggest that probably the number of declared sufferers of GDD are somewhere in the 200 range, which we interpret that the real number is in the thousands. This may be a similar incidence to severe acute allergic reactions.

6.4. Diagnosis

Diagnoses include clinical symptoms after exposure to standard dose, or greater, of any GBCA and confirmation of gadolinium retention [53]. Our current impression is that the most reliable laboratory test to confirm gadolinium deposition may be 24-h urine test, which should be performed at least 30 days after GBCA administration. The explanation for this is that we believe that 24-h urine gadolinium likely gives the best window for 'mobile' circulating gadolinium in the host, as it reflects a 24-h window. In contrast, a blood sample for gadolinium gives just a snap shot view of the circulating gadolinium at the time the test is taken, providing a vastly lesser amount of gadolinium and ignoring the likelihood of diurnal variation in gadolinium release. Testing tissues should accurately detect gadolinium, but this is more invasive, generally painful, and much more expensive. As importantly, tissues such as bone, which is the largest repository, are nonspecific, and virtually everyone who has received perhaps even a single dose of GBCA, especially if it is a linear nonionic agent, will have bone deposition (GSC), but only a small fraction of these will have GDD.

6.5. Treatment

The consideration of treatment for sufferers is early. Based on the hypothesis that GDD may be a genetic abnormality in metabolizing heavy metals, the correct treatment of this disease may entail a combination of re-chelation and immune system modulation [46].

For some years patients who have become symptomatic after GBCA, and who have felt that this arose due to the recent administration of a GBCA, have been dismissed by mainstream physicians. Our explanation is that their physicians considered that since the patients had normal renal function they could not have gadolinium toxicity, since the recognized disease, NSF, only occurred in patients with advanced renal failure. Rejected by mainstream medicine, they have had to seek out more fringe-of-medicine based therapy. Many of these patients have experienced some success with rechelation therapy, but the problem has been the lack of scientifically-guided optimization of this treatment. Chelation centers generally use ethylenediaminetetraacetic acid (EDTA) as the chelation agent, but EDTA, although showing good thermodynamic stability for smaller atomic number elements, such as calcium, is actually a rather poor chelator for heavier cations such as gadolinium. Probably the best available chelator is pentetic acid diethylenetriaminepentaacetic acid (DTPA), which has good thermodynamic stability and approximately 300,000 times more affinity than EDTA for gadolinium. The worry with EDTA therefore is that it may dislodge gadolinium from tissue stores, but may simply translocate it somewhere else in the body. In contrast, DTPA has the binding strength to not only pick up gadolinium but also retain it long enough to be removed from the body through renal excretion, which is the usual route for GBCA elimination. Other chelators have also been evaluated. Leung et al. [54] reported that deferoxamine doubled the urinary excretion of Gd, but had no effect on serum Gd levels in an NSF patient and concluded that it was too weak of a chelator for Gd removal. While not reported for Gd^{+3}, the log thermodynamic stability constant of deferoxamine for a related lanthanide, La^{+3}, is 10.9, which is many orders of magnitude lower than the log-binding constant of DTPA for Gd^{+3}, which is 22.5.

Tackling of the issue of tempering the host response to gadolinium is a more complex subject that is far from developed. Likely the optimal agent is one that has a profile for dampening release of cytokines/chemokines that best matches the profile of the cytokines/chemokines released in the presence of gadolinium. We strongly discourage random experimentation with agents. Also it appears that the vast array of various other treatments patients have tried or been subjected to, either have no effect (at best) but also cause additional harm, in addition to the underlying harm from GDD. The only ancillary treatment that may offer some benefit are simple anti-inflammatories (ibuprofen, ASA, naproxen) and antihistamines (diphenhydramine). Benefit though seems to be minimal with these. Eventually targeted immune modulators are ideal agents, which likely also will be agents with particular value to treat severe acute allergic reactions.

7. Summary

Gadolinium toxicity is a family of disorders including acute adverse reactions, NSF, GSC, and GDD. To the present time, little is known about GDD and most assumptions are hypotheses borrowed from empirical information on other disease processes. As summary, what is known is that GDD is a real entity, likely very uncommon, related to GBCA exposure, similar to NSF but seen in patients with normal renal function (also seen in those with poor function), and caused by a range of GBCA agents irrespective of their molecular structure. Our hypotheses is that the pathophysiologic mechanism is a combination or summation of acute and subacute allergic reactions (polypeptide [cytokine] and cell-based [fibrocytes, mononuclear phagocytes], respectively), gene-based, affecting European-origin Caucasians with female predominance, amenable to treatment with rechelation (almost certainly) and possibly with targeted-host-immune-modulator agents.

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