Gadolinium Deposition Disease
Current State of Knowledge and Expert Opinion

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Abstract: This review describes the current knowledge of a form of gadolinium toxicity termed gadolinium deposition disease (GDD), supplemented with the opinions of the authors developed during 6 years of clinical experience treating GDD. Gadolinium deposition disease can also be considered a subset under the symptoms associated with gadolinium exposure rubric. Young and middle-aged White women of central European genetic origin are the most affected. The most common symptoms are fatigue, brain fog, skin pain, skin discoloration, bone pain, muscle fasciculations, and pins and needles, but a long list of additional symptoms is reported herein. The time of onset of symptoms ranges from immediate to 1 month after gadolinium-based contrast agent (GBCA) administration. The primary treatment is to avoid further GBCAs and metal removal through chelation. Presently, the most effective chelating agent is DTPA because of its high affinity with gadolinium. Flare development is an expected outcome, amenable to concurrent immune dampening. We emphasize in this review the critical nature of recognizing GDD when it first arises, as the disease becomes progressively more severe with each subsequent GBCA injection. It is generally very treatable after the first symptoms of GDD, often arising after the first GBCA injection. Future directions of disease detection and treatment are discussed.

Key Words: gadolinium deposition disease, GDD, gadolinium, SAGE, flare, chelation, GBCA

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Gadolinium deposition disease (GDD), in addition to acute hypersensitivity reaction (AHR) and nephrogenic systemic fibrosis (NSF), is a form of gadolinium (Gd) toxicity. Together, these entities represent a spectrum of the symptoms associated with gadolinium exposure (SAGE). In recent years, GDD has achieved generalizability, which is a critical requirement for disease recognition. Three independent groups have reported in the peer-reviewed literature on GDD.[1–5] In this review, we will describe observations reflecting whether they have achieved broad acceptance as a theory (BAT) or if it is a novel theory/opinion of our team (NT). We also have graded the level of evidence (LOE) using criteria from the Oxford Centre for Evidence-Based Medicine[6] (Table 1).

DIAGNOSIS

The basis for the diagnosis of GDD involves 4 essential components:

1. The development of specific symptoms shortly after receiving a gadolinium-based contrast agent (GBCA) injection (Table 2).
2. The timeline of the development of symptoms: from immediately after the injection to up to 1 month afterward.
3. The symptoms were not present before the GBCA injection in patients.
4. Flare symptoms arise after the administration of a potent chelator for Gd, such as Ca-DTPA.

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Original reports on this subject relied on anonymous surveys of self-described GDD sufferers[1,7,8] or clinical evaluation of a small number of patients,[9] LOE 3b, which only described the first 3 of the aforementioned criteria. Subsequent studies described the chelation of patients with DTPA, in whom flare of symptoms arose after chelation, starting immediately to 2 days after injection,[10,11] LOE 2b. Indirectly, this finding reflects the Bradford Hill criteria[12] of symptoms reproduced when the drug is readministered: chelation draws gadolinium from the tissues back into the vascular circulation, reigniting symptoms. Establishing this Bradford Hill criterion is challenging because, in most settings, deliberately giving a drug to an individual who is allergic to it is of questionable ethics. However, in the somewhat unique case of GDD and chelation therapy, the chelation process reignites the symptoms.

More recent studies have described cytokine features related to GDD. An early study,[13] LOE 2b, observed that static nonselected measurements of cytokines differed between GDD sufferers and "normals" (control group). The control group represented recipients of a prophylactic influenza vaccine. TNF-α and IL-6 were higher in the GDD group. A follow-up study examined pre– and 24-hour post–Ca-DTPA cytokine levels in patients with GDD and subjects with a history of GBCA injection who did not become sick from it, termed gadolinium storage condition (GSC).[14] In that study, select cytokines dropped 24 hours postchelation, which may reflect select immune cells, for example, circulating preinflammatory mesenchymal cells, moving from circulation to the tissues. Hence, cytokines released by those cells would no longer be in circulation but locally deposited (NT).[15]

The most recent cytokine studies entailed obtaining dynamic serial blood draws for cytokines at 1 minute, 5 minutes, 10 minutes, 30 minutes, 1 hour, and 24 hours postinjection,[16] LOE 2b. No study of this level of dynamic acquisition has ever been performed after an initiating antigen event for any process. This pilot study showed that, in principle, this dynamic acquisition was feasible. A novel observation was that various cytokines showed different peak serum level time points. In this study, patients with recent onset of GDD were evaluated. This group was compared with a few subjects with GSC. Contrary to expectations, subjects with the highest flare ratings did not have the highest cytokine elaboration. Instead, the amount of Gd mobilized and excreted was the strongest factor for circulating cytokine elevations, regardless of the agent and whether the individuals have symptoms of GDD or not. The numbers of subjects in this study were too few to achieve meaningful results on whether the types of cytokines were different between these groups. Our opinion is that subjects with GDD release predominantly proinflammatory cytokines and other inflammatory entities: alarmins and leukotrienes, whereas, in GSC, T cells and other cells release suppressor cytokines, communication cytokines, but few proinflammatory cytokines (NT). The original hypothesis had been that cytokine release would be a simple correlation of flare reaction with increased cytokine production. Instead, the picture looks much more complex, probably similar to the extensive pattern of cytokines reported in asthma.[17] More extensive studies involving hundreds, if not thousands, of subjects would be needed to generate these quality data in GDD.

Based on these works on cytokines, our present theory is that GDD is primarily an immune-mediated inflammatory disease (IMID) that has a principal effect on tissue-resident memory T cells (NT),

which have been described as the principal mediating cell in Crohn disease[18,19] and asthma.[17] Other researchers have looked at other cell products elevated in GBCA exposure and GDD, and have shown elevated serum biomarkers for mitochondrial damage.[5,20,21]

Gadolinium Retention

Studies have reported that Gd is retained in bones for many years, possibly permanently, in all subjects receiving a GBCA injection, not just renal failure patients. The human studies were initially reported in 2004[22] with subsequent publications[23,24] (BAT). More recently, Gd retention in the brain has been recognized on MR (BAT, LOE 1b). A more recent study verified that the largest reservoirs of Gd are in bone and skin, with a much smaller total amount in the brain.[25,26] Many of these studies also mentioned that no clinical evidence of toxicity was evident. However, it does not appear that subjects were clinically followed up and inquired about the symptoms present in GDD. Our opinion is that Gd is retained in everyone who has undergone GBCA-enhanced MRI, with the majority in bone (tightly bound reservoir) and skin (more loosely bound reservoir).[25,26]

Patient Demographics

A previous study showed a prevalence of women with GDD.[7] A more recent study (nonpublished data, LOE 3b) found that most sufferers are White women of genetic central European origin. Next, the most common were men of the same genetic origin and, after that, Southern and Northern European genetic origin. Blacks and Asians also may experience this disease, but it seems rare. The genetic origin is similar to other metal disorders involving iron, specifically genetic hemochromatosis. Genetic hemochromatosis primarily involves individuals of Celtic genetic origin,[27] whereas the genetic origin of GDD seems to span from Ireland through to Northern India. We believe that GDD has a strong genetic component, as has been described for lanthanide toxicity in a yeast model.[28]

Predisposing factors are also present. In our clinical experience, individuals commonly have underlying autoimmune conditions, allergies, or sensitivities, such as multiple chemical sensitivity syndrome[29,30] and mast cell activation syndrome[31,32] (NT). Events that may cause a perturbation in the immune system within days before or after the GBCA injection are also observed, including high-potency antibiotic administration, major trauma, and major physical activity (NT). Chronic infections, such as Epstein-Barr and chronic Lyme disease, are reported in some sufferers.

Some genetic conditions are commonly observed in GDD subjects. In our clinical experience, approximately one fourth of individuals have the methylenetetrahydrofolate reductase (MTHFR) gene variant.[33] Specific GDD gene discovery is a primary focus for future investigation (see below). This may be the same gene, or interconnected network of genes as we opine must also be present for NSF and AHR, and probably in individuals who develop severe symptoms with other heavy metals such as lead (NT).

AHR, GDD, and NSF and Their Relationship

Acute hypersensitivity reaction is considered a MAST cell activation condition (BAT); NSF is caused principally by CD34+ circulating fibrocytes (BAT) (likely though it is the full complement of CD34+ bone marrow cell infiltrates [NT]), and GDD is principally mediated by tissue-resident memory T cells (NT). The different mediating cells for disease also account for the varying timeline of onset of the disease from GBCA injection: immediate AHR (the majority) instantly to up to 6 hours,[34] GDD immediate to up to 1 month, and NSF usually from 2 to 10 weeks,[35] but may occur days or even years after GBCAs exposure. This may reflect the length of time for these cell groups to mobilize into action. Overlap between these entities is relatively common; in our experience, the most common overlap is likely between AHR and GDD. Our opinion of the described "failures" to generic steroid/antihistamine postreaction for AHR[36] may reflect that the patient has a continuation of immune system response, so it initially starts as a MAST cell reaction and then persisting as primarily a T-cell dysregulation, namely GDD (NT).

Not only by timeline but also by physical manifestations, GDD shares features of both AHR[37] and NSF.[38] Like AHR, all GBCAs can result in GDD (all GBCAs represent foreign particles; hence when injected, they are potential allergens), LOE 2b.[10–12] However, there is also likely variation in each GBCA agent's immunogenicity.

Nephrogenic systemic fibrosis has definitive histological features, reflecting the profibrotic nature of the immune reaction. Acute hypersensitivity reaction and GDD are primarily proinflammatory cytokine-related diseases, so histological features are generally lacking in AHR. However, some have been documented in GDD, noteworthy

TABLE 1. CEBM Levels of Evidence (2009)

1a: Systematic reviews (with homogeneity) of randomized controlled trials
1b: Individual randomized controlled trials (with narrow confidence interval)
1c: All or none (when all patients died before the treatment became available, but some now survive on it; or when some patients died before the treatment became available, but none now die on it.)
2a: Systematic reviews (with homogeneity) of cohort studies
2b: Individual cohort study or low quality randomized controlled trials (eg, <80% follow-up)
2c: "Outcomes" research; ecological studies
3a: Systematic review (with homogeneity) of case-control studies
3b: Individual case-control study
4: Case series (and poor-quality cohort and case-control studies)
5: Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Levels of evidence regarding claims about prognosis, diagnosis, treatment benefits, treatment harms, and screening.

TABLE 2. Checklist

Symptoms of Gadolinium Deposition Disease
Fatigue
Imbalance
Cognitive impairment, including brain fog and memory loss
Pins and needles sensation (often hands)
Skin crawling
Burning sensation skin and/or deep tissue
Skin morphology changes, including progressive thickening and discoloration
Subcutaneous tissue loss (classic face and hands)
Head pain
Bone pain (rib pain classical)
Joint pain (commonly large joints like knee and hip)
Muscle fasciculation
Vision problems including blurred vision and dry eyes
Hearing problems
Gastrointestinal issues (vomiting, diarrhea, hypotonia)
Cardiac arrhythmias

subcutaneous tissue nodules. Gathings et al[39] described erythematous plaques containing sclerotic bodies in the skin, representing histologic features of NSF, after multiple GBCA administrations in a patient with normal renal function. Extremely high doses of GBCAs may trigger an NSF-like skin condition despite normal renal function.[40]

Disease Manifestations and Injuries

It is clear from animal studies that Gd, as with other lanthanide metals, may cause various physiological disruptions and tissue injuries,[41] and show prolonged retention in the body in humans[22–24] and in mice models.[42,43] The principal disease process with Gd may be an IMID that stimulates tissue-resident T cells in a cascade of inflammatory cell products, principally cytokines, that profoundly affect various neural tissues and muscles: cardiac, smooth, and skeletal. The effect on the central nervous system may explain brain fog as one of the critical symptoms of disease, the sympathetic nervous system, and peripheral nerves, causing small fiber disease,[44] which seems responsible for the pins and needles sensation.

Mitochondrial injury is a major effect of gadolinium,[21] and likely injury occurs in other intracellular organelles. Currently, there has been little evidence of Gd entering cells to any extent to damage cells directly; hence, our theory is that biochemicals produced by the host, likely primarily cytokines, create this intracellular damage, either by entering the cells directly or by interacting with cell membrane binding sites.

Another principal action is the substitution of Gd for Ca^{2+} in many physiological processes. Of particular note is the substitution for Ca^{2+} in neural synapses and actin-myosin interaction in muscle tissue, including skeletal, cardiac, and smooth types. These manifest as fasciculations and tremors (skeletal), arrhythmia (cardiac), gastroparesis, and small intestine atonia with bacterial overgrowth (smooth muscle).

Compared with other allergen-reaction type processes, such as bee stings and peanut reactions, which are brief exposures, Gd and other heavy metals have durable retention in the body. So, the source for the reaction stays for a prolonged time, many years, within the patient. This explains why chelation is necessary to ameliorate the symptoms by reducing the burden of reactogenic material in the body.

A broad range of symptoms and variations in disease distribution has been observed among sufferers. The considerable variability has made some physicians incredulous that this can be one disease or even a "real" disease. However, variation in symptoms and disease distribution is widespread in multisystem or diffuse diseases, such as systemic lupus erythematosus and atherosclerosis.

Patient Information

It has been a customary practice in MR facilities to tell patients that the GBCA leaves the body entirely in 24–48 hours. This practice should cease, as it is incorrect. A small amount of Gd is always retained, with a fraction of it probably permanently. Attention to preexistent factors should be paid. Patients should be well hydrated and cautioned against excess physical activity, probably for at least 3 days before and after MRI. If they have been previously administered a GBCA, at least in the screening form, they should be questioned about durable symptoms that may be GDD. It is not advised that first-time MRI subjects receive too dire a warning about GBCAs, as the condition is rare. In advance of the imaging study, informed consent that describes the risk more fully must include the risks of other procedures, computed tomography (CT) with radiation, and iodine contrast risk, for example. Risk assessment should be a global discussion for all subjects undergoing imaging studies. Computed tomography with iodine contrast may still be a much riskier procedure for most subjects. This is beyond the scope of this review.

Gd Measurement in the Body

Gadolinium can be measured in all tissues and bodily fluids using inductively coupled plasma mass spectrometry. Typical measurements for Gd are serum and urine. Serum provides a snapshot of the Gd passing through the vascular system at the time of the blood sample. Urine values provide a longer window/time frame of Gd moving through the vascular system.

Our preference is 24-hour urine for heavy metals, as there is likely a diurnal variation of elimination of Gd from the body, so 24 hours provides a sample window to compensate for that. This provides a 24-hour window for Gd remobilization and elimination. In North America, this test is performed by Doctors Data, Genova, Mayo Clinic, and probably other laboratories. The heavy metal panel generates a view of Gd elimination and other heavy metals, some of which may act in concert with Gd to create toxic effects, such as lead (Pb). Lead is also well removed with DTPA (unpublished results). Our standard approach is to perform 24-hour urine 1–2 days before chelation and 24-hour urine immediately after chelation on day 1 after Ca-DTPA. Ca-DTPA is the most effective chelator available for Gd. The 24-hour urine test determines how effective chelation has been and how effective it will likely be in the follow-up chelations. In general, in the early chelations (first through third), GDD that has arisen after linear GBCA administration shows a 20-fold (range, 15–70) increase in urine Gd output (measuring in microgram per 2 hours), whereas the increase is usually approximately 10-fold after macrocyclic agents (range, 5–40).[11] An explanation of how DTPA removes macrocyclic agents[10,11] needs to be established. Levering the Gd of a macrocyclic GBCA out of tissues with DTPA may represent an associative chemical reaction. Assistance with removal by DTPA, which is generally a weaker binding ligand for Gd than the administered macrocyclic ligand (except Gadovist), may be rendered by structures adjacent to the macrocyclic GBCA in the body. It might be part of a biologically assisted transchelation.

Treatment

The first treatment for GDD, as with any toxic exposure, is to prevent future exposure of the subject to the substance that is toxic to them again. That is why it is critical to recognize GDD when it first manifests in a subject so that they never receive another GBCA again. The individual becomes progressively sicker with each additional GBCA.[7–9] The subsequent GBCA-enhanced MRIs are often performed to investigate what turns out to be GDD all along, making the disease worse with each injection, LOE 2b. We believe that a sizable percentage of subjects can spontaneously recover to a considerable extent if they have received only 1-lifetime exposure to GBCA injection. Sufferers report this spontaneous near-complete recovery to take between 1 and 2 years. Symptomatic GDD is likely only the tip of the iceberg of persistent SAGE,[45,46] as this latter term, by definition, also includes AHR, NSF, and transient reactions. Many patients with GDD have a mild disease when it first manifests, so they do not show severe enough symptoms to be clinically obvious, or the symptoms are unrecognized by patients themselves or their health care practitioners. Spontaneous recovery from a 1-lifetime dose of GBCA reflects that the immune system has calmed down on its own. Because this natural self-healing occurs with some frequency, it is unclear if any of the possible proposed naturopathic, homeopathic remedies work or if the patient is recovering not because of treatment but despite treatment.

In principle, the treatment for GDD involves 2 components: (1) removing the metal[10] and (2) dampening the host immune reaction,[11] which is most critical concurrent with removing the metal, LOE 2b. Many sufferers seek the addition of detoxification.

Chelation

The removal of metal is most effectively done with chelation. Currently, the most stable Food and Drug Administration–approved

chelator is DTPA. For example, DTPA is a far superior ligand to chelate Gd than EDTA based on its log thermodynamic stability constant (log K_{therm} 22.1) compared with EDTA (log K_{therm} 17.3), which renders binding to Gd several magnitudes more tightly than EDTA (approximately 288,000 greater affinity).[47,48]

The only chelating agent experimentally shown to remove Gd is DTPA.[49] The authors used Ca-DTPA to chelate gadodiamide and gadobutrol in a rat model. Although the intent of the study was not to validate the use of DTPA to remove Gd from the brain, premortem and postmortem gadolinium quantification showed that Gd was mobilized out of brain tissue in rats who received the linear agent gadodiamide.

The principle for chelation is identical to the principle for creating the GBCA agent: the most stable chelator available is the best agent to create the most stable ligand bond to facilitate elimination. This point is empirically apparent: if stability is crucial for the GBCA, it is equally crucial for the decorporation chelator (AKA ligand). It would be unethical to administer Gd-EDTA as an MR contrast agent because of its poor stability; hence, it is similarly unwise to use it as a decorporation agent. An additional principle for chelation also applies: since the chelation of Gd should be kinetically rapid, a macrocyclic chelation therapy agent would be ineffective if it requires too long to get Gd into the macrocycle or cannot get Gd into the macrocycle in vivo at all. The DTPA-Gd reaction is swift, as it likely is with BOPTA (MultiHance ligand)–Gd reaction, with BOPTA possessing even a higher log thermodynamic stability than DTPA. This is related to the property of kinetic stability of GBCA agents but reflects reverse kinetic stability.

It is also essential to consider the cation the chelator is bound to. For example, DTPA is marketed with Ca and Zn as the bound cation. The principal difference is that Ca-DTPA has a lower stability than Zn-DTPA (log K_{therm} are 10.75 and 18.29, respectively),[47] so Ca-DTPA more readily transmetalizes with other metals than Zn-DTPA. In published results, Ca-DTPA removes approximately twice as much Gd as Zn-DTPA,[10] LOE 2b. For maximal removal of Gd or removal of radioactive heavy metals (eg, plutonium), Ca-DTPA may be preferred. Ca-DTPA also removes native metals such as Mg, Mn, and Zn, because these metals create a more stable bond with DTPA than Ca. Fear of the safety of Ca-DTPA has been raised, but this is the general fear that should be associated with any drug that works effectively, such as heparin and clotting inhibition. Ca-DTPA likely should not be administered more frequently than has been reported for Gd removal, which is at a 1- to 4-week interval.[10]

This would be different for radioactive metals, where the importance of rapid removal outweighs the risk of electrolyte imbalance (NT). It has been reported that Ca-DTPA administered as short as weekly has not resulted in electrolyte imbalance,[10] LOE 2b. Our routine is for chelation sessions to be spaced 3–4 weeks apart. Standard maximal chelation uses 1 g (5 mL) Ca-DTPA day 1 and 1 g (5 mL) Zn-DTPA the next day, as day 2 of a 2-day regimen: Ca-DTPA day 1, Zn-DTPA day 2 (Fig. 1).

The stability of a new drug from HOPO Therapeutics (HOPO-101) is even greater than that of DTPA with Gd. However, it is an investigational drug product that the Food and Drug Administration has not approved for clinical use. When available, if equally safe, the ease of use (orally administered) would make it an ideal chelation agent.[50] The near future for chelation might include high-stability oral chelators, HOPO, and oral DTPA and variants.[51] The ease and broad practicability of administration of oral chelators are self-evident and will greatly expand access to, and hence the market for, chelation. Because the GBCA was administered intravenously, much of the deposited Gd is in perivascular interstitial tissue distribution. Chelation for Gd should, likely also in the future, start with initial intravenous (IV) administration to capture much of the Gd in the perivascular tissue. Oral chelation is likely not as effective in removing perivascular Gd. However, once several IV chelations have been performed and a fair amount of the perivascular Gd is removed, oral chelation may be preferred to continue treatment (NT).

The use of immune dampening with concurrent steroids and antihistamines is imperative for most subjects with GDD. Principally, this is to dampen the flare reaction, LOE 2b. However, we also consider its effect essential to train the immune system to stop reacting to Gd by

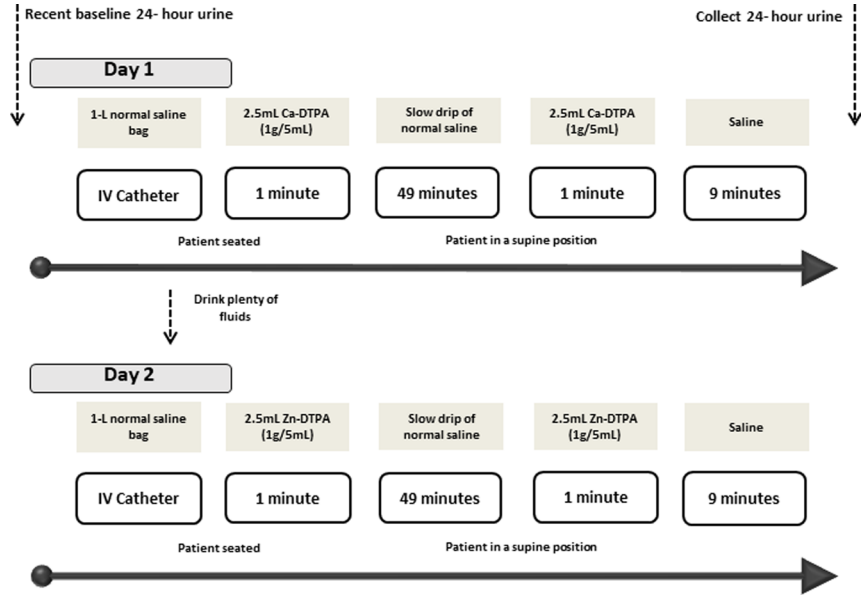

FIGURE 1. EHMR (extended hypersensitivity medication regimen) entailed administering 3 drugs in the following schedule: 2 days before chelation: methylprednisolone 8 mg tablet by mouth twice daily; then 3 times per day for the 2 days of chelation, and 1 day after (the second of the 3 doses 30 minutes before chelation, and at noon on the day following chelation); then in the morning and night on day 2 and 3 after chelation, and just the morning on day 4 and 5, for a total of 9 days. Desloratadine 4 mg by mouth began 2 days before chelation and continued for 9 days. Montelukast 10 mg by mouth at night beginning 2 days before chelation and continuing for 9 days. Desloratadine/Montelukast may be continued beyond the ninth day. If adverse effects to montelukast are present replace with Desloratadine. Hydroxyzine is an alternative antihistamine regimen. Methylprednisolone is discontinued after the ninth day.

diminishing the tendency for immune cells to react vigorously to Gd movement, both out of tissues and in transit through the vascular system on removal (NT). Our standard protocol is shown in Fig. 1.

The concurrent steroid/antihistamine approach is identical to the principle of treating contrast reactions with iodine contrast in CT, Gd contrast in MR, and managing drugs with high rates of hypersensitive reactions in oncology. The modifications we use are to start 2 days before chelation and carry through the 2 days of chelation to 5 days afterward, for 9 days. In practical terms, this represents an acute hypersensitivity drug regimen combined with a steroid taper.[11] This approach is superior to no concurrent immune dampening, antihistamines alone, and better than beginning immune dampening after the reaction has begun,[11] LOE 2b. Our current approach is adding IV steroids and antihistamines in selected individuals with a very high likelihood of severe flare, which includes chelation treatment within 3 months of GDD development, individuals who have received multiple GBCA injections, and patients exhibiting severe symptoms of GDD at the time of chelation. In addition, our current practice is to start with a lower amount of chelation for the first session to observe the severity of the flare reaction, and to acclimatize patients to the experience of a flare, so they are less anxious with future greater flare reactions, which are expected when a larger amount of chelator is used. As subjects undergo more chelation sessions (generally >5), flare reactions progressively diminish in severity primarily because less Gd is left in the body to generate flare on its removal.

Ancillary/Supplemental Treatments

Ancillary elimination pathways, such as sweating, are likely of additional benefit in some. Caution must be paid, and the individual should start with short sessions when trying sauna. Some patients with GDD have lost the ability to sweat and should not undergo sauna, as this will exacerbate their symptoms since the body will experience elevated temperature because of the absence of the ameliorating effect of sweating. This elevated core temperature results in metabolic acidosis, which aggravates the symptoms of GDD. Hyperbaric oxygen therapy has shown benefits in some sufferers.

Low-dose naltrexone has shown some benefits in GDD patients. Interestingly, a recent investigation with 5 GDD patients showed that pain was improved in those who received IV Ca-DTPA chelation and low-dose naltrexone.[52]

The future role of more potent immune dampening, such as disease-modifying antirheumatic drugs,[53] or with specific treatment of select Gd injuries, such as mitochondrial injury, has yet to be established.

Supplements, dietary modifications, and physical treatments all play a role in the treatment of patients. Selected ancillary treatments should be considered if they are scientifically plausible to have benefits, affordable, and very unlikely to cause harm. It is also essential to be attentive; some ancillary treatments that work well for some may harm others; as mentioned previously, sauna is one example.

Generally, consuming foods or supplements that are fundamentally anti-inflammatory makes good sense, so turmeric, spirulina, and chlorella are examples. Expansion on this is beyond the scope of this review. Nevertheless, one should be very cautious, and adding supplements one at a time is prudent.

Flare

Disease-related flare occurs spontaneously and is common. Sufferers often show dramatic day-to-day or diurnal variation in the severity of disease-related flares.

Treatment-related flare has 3 forms: Gd removal, redistribution, and re-equilibration. This discussion is based on our 6-year clinical experience with treating sufferers with chelation.

Gadolinium removal flare generally arises immediately to 2 days after DTPA/chelator injection. Its severity needs to be controlled. The development of flare after a potent chelator is a critical feature to confirm that the patient has GDD. If there is no Gd removal flare in early chelation sessions to a potent chelator, there is no GDD. Flare is the reintensification of the initial symptoms of GDD. Flare may occur in a different site than where the pain was appreciated when the disease first arose, such as in the left ribs when the original pain was in the right ribs. Uncommonly, the flare may involve a new type of symptom that is part of the symptom complex of GDD. New development of tremors, for example, flares, generally settle down at approximately 1 week after chelation if using the combined steroid regimen. Gadolinium removal flare arises due to the removal of Gd from tissues; recognition of this movement provides tissue-resident T cells the impetus to release proinflammatory cytokine, and possibly cytokine release arises from the recognition of an increased quantity of Gd in the vascular circulation. With chelation, the majority of Gd is removed from less tightly bound reservoirs: skin and White blood cells in the spleen, lesser amounts from soft organs (such as in the brain, heart, liver, and kidneys), and a small amount from the tightly bound reservoir of bone (NT). The latter is observed only with strong chelators (eg, DTPA).

Redistribution flare arises when a less potent chelator is used (DMSA, DMPS, EDTA), reflecting that a relatively large amount of the Gd that is picked up in the tissues is rereleased relatively quickly before the Gd has left the body. This is because the stability of the Gd with the chelator is relatively poor. This flare arises in tissues where the redistributed Gd has been deposited (eg, picked up in the skin, redistributed in the brain). The redistribution flare arises immediately to within 1 week, which is the same timeline as the Gd removal flare. Unlike flare from Gd removal, this is an undesirable flare. This can be avoided by using a strong chelator that results in a negligible rerelease of Gd back into the body.

Re-equilibration flare is the third form of posttreatment flare. This phenomenon is le Chateliere's principle: everything strives to be in equilibrium. So, when much of the Gd is removed from the skin, Gd moves from bone back to the skin, and other soft organs, to re-equilibrate (NT). Re-equilibration flare begins at 1 week but becomes prominent at approximately 3 weeks. If no subsequent chelation is performed, it generally continues to escalate for at least 3 months, at which point it can reach a plateau, decrease, or continue to escalate (NT). This phenomenon explains why chelation must be used as a multiple repetition therapy to facilitate removal from bone by repetitions of le Chateliere's principle and thereby escalate depletion of total body Gd content. For most sufferers, at least 5 chelation sessions are needed so that several re-equilibration phases have been experienced. The Gd flux of the re-equilibration process is lessened with each further chelation, reflecting that total Gd body content is decreased, so the symptoms of flare diminish, but this is generally not a linear decrease. The chelation treatment likely also benefits from the spacing between chelation sessions, as the periods of re-equilibration facilitate the removal of Gd from tightly bound reservoirs such as bone (NT). Hence intervals from 1 to 4 weeks seem ideal to achieve some re-equilibration but not excessive. Attention to the time of onset of re-equilibration flare is critical, as chelation should be performed within a few days of re-equilibration symptoms, as these symptoms progress in severity (NT).

Prognosis

In our clinical experience, the prognosis of individuals who have received less than 3 GBCA injections and are treated with the DTPA/steroid regimen is good. At least 75% will experience at least 80% improvement after 5 chelations sessions, and 50% are near-cured (NT). This compares favorably with many medical treatments. Some response is achievable in most patients, even those who have received multiple GBCA injections or have other complications or additional diseases. In those who have received approximately 10 GBCAs, many will achieve some recovery, but it may require more chelation sessions, often greater than 20, for significant improvement. Many patients with other preexistent T-cell dysregulations also do well, as part of the treatment (eg, steroids) has

an effect against their additional condition (eg, COVID long haul). General metal removal by chelation also directly benefits other diseases that may also be caused by heavy metals, such as fibromyalgia.[54,55] Up to 5% of subjects with unknown types of preexistent T-cell dysregulation or other severe conditions may not benefit from chelation, and chelation may worsen the condition (NT). This is under investigation.

GDD Masquerading as Other Conditions

A significant health care risk arises because T-cell dysregulation conditions predispose to other T-cell dysregulation conditions (NT). So entities such as fibromyalgia, once they start undergoing MRI with GBCA,[54] may become primarily GDD. A present-day situation that may achieve significant health care risk is that sufferers with the common entity of COVID long haul, and less common but still important COVID vaccine long haul, may likely undergo several MRIs to investigate their disease. As these long-haul conditions are likely both T-cell dysregulations, our opinion is that they predispose the individual to develop GDD (NT). Attention will need to be made to determine whether symptoms believed to represent these long-haul conditions may be GDD. At least GDD can be effectively treated.

Criticisms of GDD

"Opinion lies in the vast wasteland between ignorance and wisdom."—Plato

There are criticisms in the literature regarding the disease[56,57] and the treatments.[58] Nevertheless, the authors of these critiques seem to have no or limited experience with individuals with the disease and none with the treatment of the disease, particularly with the protocols we use (LOE 5).

There are valid criticisms, as with any disease early in the investigation, especially when rare. Gadolinium deposition disease is a relatively uncommon disease, possibly with a similar occurrence rate as severe AHR. We estimate that 1 in 10,000 subjects who undergo GBCA-enhanced MRI develop GDD, and 1 in 100,000 severe GDD (NT), comparable numbers for AHR, which is not surprising as they have similar immune reactions (NT). We derive these estimates based on the estimated number of patients with the disease by accessing Gd toxicity group Internet sites, the number of GBCA injections performed annually in the United States and worldwide, and reference to data on AHR. To date, no effective alternative treatment exists compared with DTPA with concurrent immune dampening. Performing a randomized controlled trial (RCT) with an inferior and possibly dangerous alternative such as EDTA chelation is ethically questionable. The reported protocol of DTPA with concurrent immune dampening is a viable arm for future RCT with a presumed effective agent, such as with HOPO, when it becomes available.

As reported with NSF, consistent histologic findings have not been reported in GDD. One report described Gd-associated fibrosis in individuals with normal kidney function,[36] which is GDD. In our clinical experience, we have observed subcutaneous nodules, which arise in individuals after GBCA injection, decrease and/or disappear after chelation (NT).

Global Health Care Benefits to the Study of GDD

Gadolinium deposition disease is an excellent example of a severe immune reaction of IMID type. All patients develop flare with effective chelation. Hence, this model can examine different strategies of hypersensitivity medicine regimens. To date, all protocols for hypersensitivity reactions are based on pure empiric reasoning. Treatment-related flare reaction from chelation provides a setting where relatively few patients would be needed to evaluate regimens (50–100 range) rather than the tens of thousands for standard severe adverse reactions and the millions needed for very severe reactions. Gadolinium deposition disease also differs from all other metal toxicities in that the dose of the metal received is knowable.

Studying individuals who have undergone GBCA injection and have not developed GDD (GSC) may also be critically important. How do most individuals who receive a GBCA not develop a strong immunological reaction? Dismissing the existence of the GDD reaction, by extension, dismisses the importance of determining why GSC subjects do not experience this. Hence it hampers the critical investigation into the protective mechanisms present in GSC individuals that are absent or deficient in GDD. This scientific knowledge should provide valuable insights into host defense mechanisms not only for GDD but also for other heavy metal toxicity and other IMIDs, and even potentially against other diseases like cancer and infection. The study on dynamic cytokine analysis in GDD and GSC[16] is an early step in this direction.

Future Directions

1. Gene detection for the GDD (and probably related) genes
2. Continued improvement in treatment; stronger chelating agents; more targeted immune dampening to tissue-resident memory T cells
3. Screening patients for preexistent GDD before repeating GBCA injection, achievable now
4. Screening patients for the propensity for GDD development before the first GBCA injection, achievable now in a basic fashion by recognizing the risks. In the future, it will be achievable with gene testing through a buccal smear or blood test.
5. Novel treatments; fundamental advances: more effective and more specific disease-modifying antirheumatic drugs; more effective direct treatments for injuries such as mitochondria
6. Novel advances: chimeric antigen receptor T cell or chimeric antigen receptor macrophages focused on suppressing and not facilitating destruction. mRNA insertions to achieve the same goal, turning off the key to react to Gd.

SUMMARY

Gadolinium deposition disease is a disease entity that has been slow to achieve clinical recognition. Clinicians, radiologists, and MR technologists must be aware of it to prevent individuals with the disease from receiving further repeat GBCA injections, which always worsen the condition. Effective treatment exists, so GDD is a treatable, recoverable disease process for many sufferers. Insight into GDD has the prospect of revealing insights into other disease processes, starting with other heavy metal toxicities.

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