CASE IN POINT

Gadolinium Deposition Disease: A Case Report and the Prevalence of Enhanced MRI Procedures Within the Veterans Health Administration

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Background: Gadolinium (Gd) usage in the Veterans Health Administration is increasing and patients with renal disease are frequently exposed. Gd is not entirely eliminated within 24 hours after administration, which may pose long-term adverse effects.

Case Presentation: A Vietnam-era veteran aged > 70 years presented for evaluation of Gd-based contrast agent–induced chronic multisymptom illness. In the course of his routine clinical care, he was exposed to repeated Gd-enhanced magnetic resonance imaging studies. After his second Gd-based contrast agent exposure, he noted rash, pain, headaches, and hoarseness. Years after the exposure to the contrast agents, he continued to have detectable Gd in urine and serum.

Conclusions: Practitioners should be aware of long-term intracellular Gd retention (including the brain) as patients increasingly turn to consultants with concerns about Gd deposition disease. Data from patient advocates demonstrate that Gd is eliminated in intermediate and long phases, which may represent a multicompartment model. The commercialization of Gd use in imaging studies is outpacing the science addressing the long-term consequences of harboring this alien, toxic, nonphysiologic rare earth metal.

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Gadolinium (Gd)-based contrast agents are frequently used in health care for enhancing magnetic resonance image (MRI) signals at low concentrations. Contrary to popular opinion, this widely used heavy metal is not biologically inert. Once notable for its safety profile, there is mounting evidence for Gd deposition in various organ systems of the body, even in those with normal renal function. A large knowledge gap remains concerning the potential harms of Gd deposition and the factors determining its elimination from the body. However, the findings of deposited Gd throughout various organs and their intracellular compartments even years after the initial exposure have been established. Here, we describe a case of a Vietnam-era veteran whose presentation, clinical, and laboratory findings were consistent within the spectrum of Gd deposition disease.

CASE PRESENTATION

A Vietnam-era veteran aged > 70 years presented for evaluation of Gd-based contrast agent–induced chronic multisymptomatic illness His medical history was significant for chronic low back pain, chronic hypertension, type 2 diabetes mellitus, and hypogonadism. Surgical history was notable for back surgery (24 years prior), laminectomy (2 years prior), shoulder replacement (2 years prior), and an epidural complicated by a hematoma (1 year prior). His presenting concerns included a painful and pruritic rash that worsened with showering, pain originating at the right Achilles tendon with migration to the knee, and shoulder pain. His symptoms started shortly after receiving multiple exposures to Gd-based contrast agents to enhance MRIs during his clinical care (Omniscan 20 mL, Omniscan 20 mL, and Gadovist 10 mL, administered 578, 565, and 496 days prior to the clinic visit, respectively). New onset headaches coincided with the timeline of symptom onset, in addition to hoarseness and liberation of an "oily substance" from the skin. More than one year prior to this clinic visit, he was considered for having polymyalgia rheumatica given the ambiguity of symptoms. Functional status remained impaired despite treatment with prednisone and methotrexate.

The patient's military service was in the mid-1960s. He was deployed to Japan and had no knowledge of an Agent Orange exposure. His tobacco history was distant, and he reported no tattoos, prior transfusions, or

occupational metal exposure (he was never stationed at Camp Lejeune or other bases with potential toxicants in the drinking water). Family history was significant for lung cancer in his mother (smoker) and his father died aged > 90 years. One sister had fibromyalgia. The patient's children were healthy.

Clinical Findings

The patient was afebrile, normotensive (146/88 mmHg), and normocardic. His weight was 100 kg. He was well nourished and in no acute distress. The thought process was attentive, and his affect pleasant. Ocular examination was notable for arcus senilus. The fundoscopic examination was limited on the left, but there was no neovascularization on the right. Jugular venous pulsation was normal at 8 cm. Right ventricular impulse was slightly hyperdynamic, the rhythm was regular, and there was no abnormal splitting of S2. A soft-grade I/VI crescendo/decrescendo murmur was auscultated along the apex. Radial pulses were 2/2. He was not in respiratory distress, with equally resonant fields bilaterally. Lung sounds were clear bilaterally. A papular, erythematous rash was present in a general distribution over the chest, with few telangiectasias and some varicosity along his left arm. The skin had normal elasticity, although the skin of the hands and legs was papyraceous.

Gd levels were measured in the blood and urine (Table 1). Gd was detectable in the skin (0.2 µg/g) nearly 400 days after the last exposure. Gd was still detectable in the patient's blood and urine (0.2 ng/mL and 0.5 µg/24 h, respectively) more than 3 years after his last exposure.

TABLE 1 Prior Laboratory Values

Days Prior to Visit	Creatine Levels, mg/dL[a]	Days Prior to Visit	Creatine Levels, mg/dL[a]
23	1.30	564[b]	1.10
84	1.50	569	1.08
100	1.76	572	0.95
445	0.90	573	0.99
458	1.08	575[b]	1.10
486	1.4	592	1.09
487	1.6	737	1.05
488[b]	1.6	**Days Prior to Visit**	**Gadolinium Levels**
533	0.97	65	Skin, 0.2 µg/gm
534	1.17	360	Serum, 0.4 ng/mL
554	0.99	360	Urine, 5.2 µg/24 h
560	0.96	429	Serum, 0.7 ng/mL
563	1.05	429	Urine, 15 µg/24 h

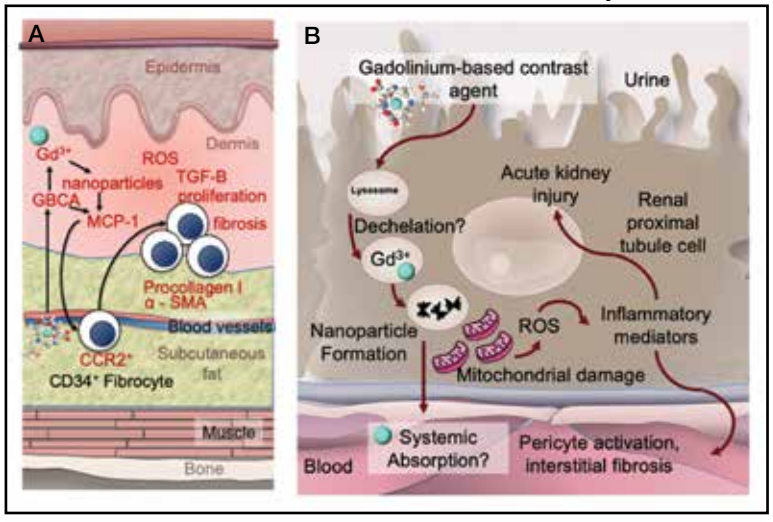
[a]Units can be converted to µM by multiplying by 88.4.
[b]Gadolinium-based contrast agents were administered 578, 565, and 496 days prior to the clinic visit.

DISCUSSION

In the United States, there are 40.44 MRI units per million people and 40 million MRIs are conducted annually. From 30 to 50% of these are enhanced with Gd-based contrast agents. In the past 30 years, there have been > 450 million contrast-enhanced MRI procedures.[1]

Gd is a rare earth metal. Among commercially available elements Gd has exceptional properties for enhancing MRI signals at low concentrations.[1] The nonphysiologic metal is detoxified by chelation with proprietary multidentate formulations that enhance (primarily renal) elimination while retaining the paramagnetic and chemical properties for imaging. Gd exposure was found to be associated to iatrogenic nephrogenic systemic fibrosis in 2006 and later confirmed via multiple systematic reviews.[2] Gd is retained in every vital organ after exposure.[3] Gd-based contrast agents stimulate bone marrow–derived fibrocytes in mediating fibrosis, and bone marrow develop a memory of prior contrast exposure (Figure 1).[4-6] Systemic fibrosis is mediated by the monocyte chemoattractant protein 1/C-C chemokine receptor 2.[6,7] Even in the setting of normal renal function, Gd-based contrast induces the formation of Gd-rich nanoparticles in the skin and kidney.[7,8] Far from being inert, Gd-based contrast agents induce systemic metabolic changes such as hypertriglyceridemia, elevations in low-density lipoprotein cholesterol, insulin resistance, and the Warburg effect (glycolytic/energy switching) in the renal cortex concomitant with profound mitochondrial abnormalities.[8]

FIGURE 1 Gadolinium-Based Contrast Agent–Induced Mechanisms of Disease in the Skin and Kidney



Abbreviations: α-SMA, α-smooth muscle actin; CCR2, C-C chemokine receptor 2; GBCA, gadolinium-based contrast agent; Gd, gadolinium; MCP-1, monocyte chemoattractant 1; NADPH, nicotinamide adenine dinucleotide phosphate; Nox4, NADDPH oxidase 4; ROS, reactive oxygen species; TGF-β, transforming growth factor β.

A, Elsewhere we have demonstrated that Gd-based contrast agents are retained in the skin. This may or may not proceed to dechelation of Gd. We have found nanoparticles in multinucleated giant cells in the skin.[7] Bone marrow–derived, CD34+ fibrocytes bearing the CCR2 infiltrate the dermis in response to liberated MCP-1. These fibroblast precursors express procollagen type I, the activated myofibroblast marker α-SMA stress fibers, Nox4-derived ROS, concomitant with an increase of pro-fibrotic TGF-β, proliferation markers (Ki67), and histologic fibrosis.[3-6,26] B, Gd-based contrast agents have been known to be injurious to the kidney since approval for use in humans. We have discovered that systemic treatment with Gd-based contrast agents culminates in nanoparticle formation within lysosomal vesicles—evidence that there is dechelation in vivo.[7,8] Gd induces renal proximal tubular mitochondriopathy, the generation of Nox4-derived ROS, and metabolic switching (ie, the Warburg effect) concomitant with tubular damage and infiltration of bone marrow–derived cells.[8,26] Graphics courtesy of Brent Wagner.

We have discovered that the rate of Gd-enhanced procedures has increased immensely within the Veterans Health Administration (VHA) system in a subset of patients with designated kidney disease (Table 2). Although a substantial number of procedures are dedicated to head and brain imaging within the VHA, the indications for Gd-enhanced diagnoses (eg, cardiac) are increasing (Figure 2).

Retention of Gd can be modeled as a function of time (t) by the half-lives of the fast, intermediate, and slow phases of elimination (T_a, T_b, and T_c, respectively):[9]

$$Retention = Ae^{\left(\frac{-0.693}{Ta}\right)t} + Be^{\left(\frac{-0.693}{Tb}\right)t} + Ce^{\left(\frac{-0.693}{Tc}\right)t}$$

A, B, and C are the proportions (adding to 100%) that represent each of the compartments: quickly, intermediately, and slowly equilibrated spaces. The rate constants for renal elimination from the plasma (K_{P0},) flux from the fast space to plasma (K_{FP}) and from the slowly equilibrated space to plasma (K_{SP}) are components of the total Gd elimination from these compartments, respectively (Figure 3). It is improbable that Gd is liberated from the multidentate formulations that constitute MRI contrast agents given the relatively high affinities for the toxic lanthanide metal, the low volume of distribution, and the rapid—essentially entirely renal—elimination rates (Figure 4). Nonetheless, Gd is retained long-term in subjects with normal renal function, in symptomatic patients, permanently in the brains of patients, and in every organ we have tested with our animal models.[3,7,8,10-12] Patients with normal renal function continue to report symptoms attributed to Gd-based contrast agents concomitant with retarded elimination.

Numerous patients with normal renal function developed similar or novel symptoms that have been attributed to Gd concomitant with detectable urinary Gd years after exposure.[11] Gd-based contrast agents are increasingly associated with cutaneous abnormalities even outside of nephrogenic systemic fibrosis. Gd-associated plaques develop in patients without kidney disease—these range from asymptomatic, pruritic, to burning.[13] Histologic specimens reveal CD68 and factor XIIIa–positive spindle-shaped myeloid cells (the same mediators of iatrogenic systemic fibrosis) or CD34-positive cells. CD68 and factor XIIIa are distinctive for histologic specimens from patients with systemic fibrosis, and these markers have been detected in our preclinical models that demonstrated that bone marrow–derived cells are involved in mediating fibrosis.[3,4,14-19] Similarly, CD34-positive cells have been historically associated with systemic fibrosis lesions.[15,16,18-23] Plump osteocyte-appearing cells have also been noted (note that extraosseous metaplasia makes the histologic diagnosis of systemic fibrosis).[14] Nephrogenic systemic fibrosis is an iatrogenic disease that can manifest years after exposure to Gd.[5] Gd induces the recruitment of bone marrow–derived cells to the affected sites.[4]

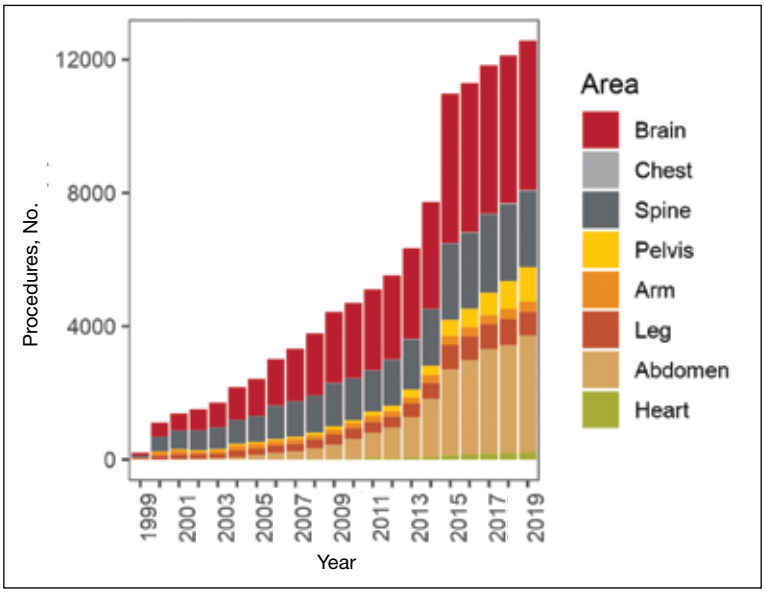
The VA Health Service Research and Development Evidence Synthesis Program reviewed the safety of Gd-based contrast agents in patients with impaired kidney

TABLE 2 2019 Magnetic Resonance Imaging Procedures With Contrast for Patients With Kidney Disease in the VA[a]

HCPCS Codes	Descriptions	VA Orders, No.
70542	MRI of bones of the eye, face, and/or neck with contrast	678
70543	MRI of bones of the eye, face, and/or neck before and after contrast	6755
70545	MRA of head blood vessels with contrast	388
70546	MRA of head blood vessels before and after contrast	700
70548	MRA of neck blood vessels with contrast	1733
70549	MRA of neck blood vessels before and after contrast	3817
70552	MRI of brain with contrast	2910
70553	MRI of brain before and after contrast	76,930
70559	MRI of brain, during open brain procedure before and after contrast	257
71552	MRI of chest before and after contrast	627
72142	MRI of upper spinal canal with contrast	872
72147	MRI of middle spinal canal with contrast	596
72149	MRI of lower spinal canal with contrast	1788
72156	MRI of upper spinal canal before and after contrast	10,384
72157	MRI of middle spinal canal before and after contrast	7229
72158	MRI of lower spinal canal before and after contrast	16,930
72196	MRI of pelvis with contrast	2163
72197	MRI of pelvis before and after contrast	17,901
73220	MRI of arm before and after contrast	3610
73222	MRI of arm joint with contrast	2562
73223	MRI of arm joint before and after contrast	2250
73719	MRI of leg with contrast	238
73720	MRI of leg before and after contrast	7193
73722	MRI of leg joint with contrast	1015
73723	MRI of leg joint before and after contrast	3650
74182	MRI of abdomen with contrast	964
74183	MRI of abdomen before and after contrast	50,636
75561	MRI of heart before and after contrast	2437
75563	MRI of heart before and after contrast with stress imaging	299

Abbreviations: HCPCS, Healthcare Common Procedure Coding System; MRA, magnetic resonance angiograph; MRI, magnetic resonance image; VA, US Department of Veterans Affairs.
[a]A data repository (1576574-1, H-6574 Wagner, IRB approval 2020-09-16, R&D Committee approval 2020-09-24) was established for patients with HCPCS codes indicating kidney disease (ICD10 N17.*, N18.*, and N19.*, N99.0, O90.4, O00, O07, O08.4, R39.2, T79.5, O90.4, K76.7, D59.3, R39.2, N14, P96.0).

FIGURE 2 Gadolinium-Enhanced Procedures Increase Within Veterans Health Administration Facilities



In 2019, there was a mean (SD) 668 (366) procedures daily in a subset of patients with prior or current acute, chronic, or congenital renal disease; > 50% were exposed multiple times.

function.[24,25] The group found only a single study of Gd and veterans. "Awareness and concern are growing about the long-term deposition of gadolinium in [the] brain and other tissues among patients with normal kidney function," according to Lunyera and colleagues.[25] The largest knowledge gap was that a comprehensive review "of all potential harms associated with gadolinium exposure" was not addressed. Furthermore, the group advised "caution in the use of [Gd-based contrast agents] in patients with severely impaired kidney function and acute kidney injury remains prudent, because the exact clinical factors contributing to [nephrogenic systemic fibrosis] risk in these subpopulations are still unknown."[25]

Gd-based contrast agents—contrary to a widely held misconception—are not biologically inert.[1] Gd-based contrast agents have a long history of association with acute renal injury. We have demonstrated that systemic treatment with MRI contrast agents leads to vacuolization of the proximal tubule and tubular injury.[7,8] Kidney injury may be mediated by the generation of reactive oxygen species from NADPH oxidase 4 (Nox4).[26]

Gd retention, Gd-induced multisymptomatic illnesses, Gd-associated plaques, Gd-induced neurotoxicity, and nephrogenic systemic fibrosis are part of a continuum (with Gd as the common thread)—a theme of the September 8, 2017, US Food and Drug Administration (FDA) Medical Imaging Drugs Advisory Committee meeting.[27] Patients, patient advocacy groups, and regulating agencies are concerned about long-term retention of a nonphysiologic rare earth element such as Gd.[28-30] A patient advocacy group, The Lighthouse Project, collected information from patients linking the last date of Gd-based contrast agent exposure and urinary Gd.[11] Data from their report suggest that the rate constants (valuable for the elimination equation above) are obtainable from 24-hour urine collections. Conceptually, Gd-induced diseases may represent a continuum that results from the retention of a nonphysiologic, toxic heavy rare earth metal.

As a heavy metal, Gd is not a natural physiologic trace element. Similar to numerous nonphysiologic metals, Gd is toxic. Inhaled Gd oxide (Gd_2O_3) dust leads to a number of time-dependent pathologies. Animal lung studies demonstrate reduced elasticity, enlarged cells, thickened lung walls, and recruitment of immune cells.[31] Symptoms of acute IV Gd toxicity include decreased respiration, lethargy, abdominal cramps, and diarrhea.[32] Pharmacologically, Gd concentrates in the liver and kidney and accumulates in the bone.[32] Animals demonstrate intestinal depression and low blood pressure in response to Gd and, with higher doses, cardiovascular collapse.[32] IV Gd chloride leads to metal deposition in the small blood vessels diffusely throughout the body, particularly in the lung and kidney and the metal is absorbed by the scavenging white blood cells.[33] Gd chloride induces severe damage to the liver, spleen, and the digestive tract.[33] Furthermore, this form of the toxicant metal markedly impacted functions associated with bleeding and clotting, ie, decreased platelet numbers and an increase in the laboratory-measured coagulation parameters.[33] Semelka and colleagues have characterized chronic symptoms attributed to Gd-based contrast agents (not limited to chronic pain, headache, bone pain, skin thickening, and clouded mentation).[34,35] Because Gd-induced conditions are underrecognized and ill-defined, disinherited patients often resort to

untested (and potentially dangerous) chelation therapies.[36]

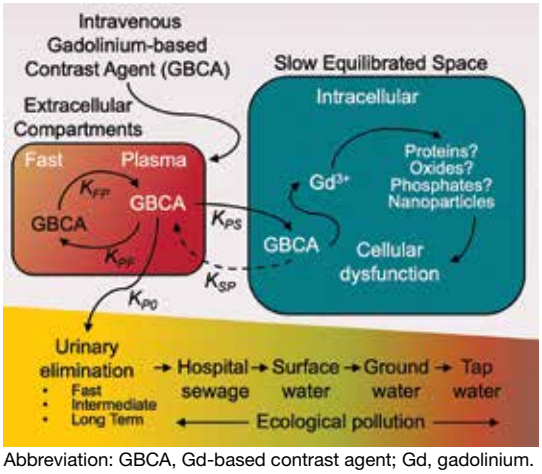
This patient presented with numerous symptoms that arose after Gd exposure. It is well established that Gd-based contrast agents (of any class) are retained in multiple organs (including the brain), for months to years. Gd-based contrast agents enter the cerebrospinal fluid within minutes of IV administration.[37] Gd was found in the cerebrospinal fluid 9 months after administration in a case presented to the FDA Medical Imaging Drugs Advisory Committee.[38] We know from intentional and accidental intrathecal administrations that Gd-based contrast agents are neurotoxic.[39] Runge and colleagues demonstrated that Gd-based contrast agents exert mitochondrial toxicity in cultured neurons in vitro.[40] McDonald and his team found Gd-rich nanoparticles within the brain neurons (cytoplasm and nuclei) from patients exposed to MRI contrast in the normal course of care.[41] These nanoparticles are similar to what we have found in rodent models of Gd-induced disease.[7,8,42]

Prolonged elimination of Gd after MRI contrast administration (months to years) may be universal.[10] Gd compartmentalizes into leukocytes and erythrocytes and into the cerebrospinal fluid within minutes.[37,43] Patients with multisymptomatic illnesses attributed to Gd (Gd deposition disease) have perturbations in cytokine levels, many inflammatory.[44,45] The results are concerning: Gd is retained intracellularly in vital organs, including brain neurons. It is inarguable that Gd is an alien, nonphysiologic element. With mounting evidence that Gd retention has clinical consequences, patients should be provided proper informed consent. Complications of renal insufficiency (ie, hyperkalemia, hyperphosphatemia, renal osteodystrophy, hyponatremia, anemia, immunosuppression, etc) follow a smooth, curvilinear slope as the true (not estimated) glomerular filtration declines; the worst iatrogenic complication from Gd—systemic fibrosis—is likely no different.

Patient Perspective

"Seems like it's one thing after another. My family doctor said that once I had the gadolinium exposures, I have had problems ever since that I don't recover from." This includes chronic numbness from the rectum to the bilateral lower extremities and an indolent worsening kidney function; "I have already developed stage 3B chronic kidney disease." Similar to many suffering with gadolinium retention, the patient was concerned about the long-term consequences. Gadolinium "is a toxic metal that is going through my body for 4 years. That has to be a problem. How come we don't have that answer?" Clinician ignorance of Gd-induced complications and long-term retention is frustrating. "Not one of my doctors has taken gadolinium retention seriously. Where else are patients supposed to go?"

FIGURE 3 Most of Gadolinium-based Contrast Agent Remains Extracellular Post-IV Administration

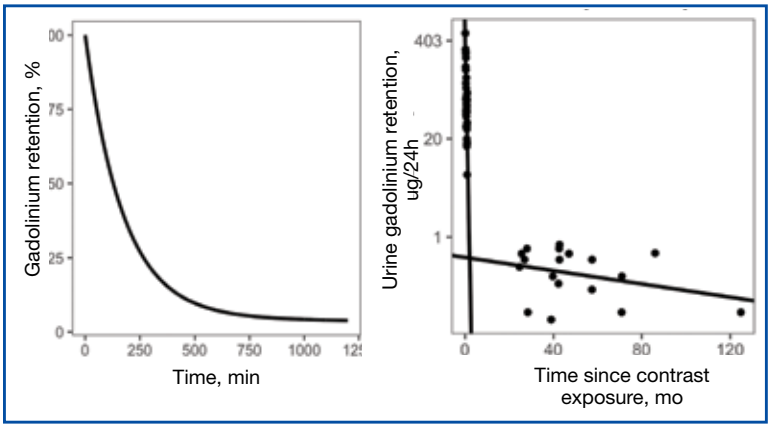


Abbreviation: GBCA, Gd-based contrast agent; Gd, gadolinium. Extracellular compartments include the plasma and the fast-equilibrated space (rate constants, K_{PF}, K_{FP}, respectively). Growing evidence shows that formulations are incorporated intracellularly where Gd is potentially liberated—the slow-equilibrated space (rate constants, K_{PS}, K_{SP}, respectively). Renal elimination (K_{P0}) of Gd is intermediate (> 54 d), and long-term (ie, years) in patients (regardless of renal function).[10,11,26] Some Gd-based contrast agent may remain intact in the tissues years after exposure (similar to a "forever" chemical, harbored intracellularly with ill-defined effects on normal physiology).[46] Some Gd is dechelated from the proprietary pharmaceutical and likely rapidly complexes into compounds that comprise the nanostructures found in patients and in our models.
Graphics courtesy of Brent Wagner.

CONCLUSIONS

Health care professionals should be considering subclinical manifestations of nephrogenic systemic fibrosis or open to considering that intracellular neuronal retention of Gd may correlate with symptoms arising after MRI contrast exposures.

FIGURE 4 Renal Elimination of Gadolinium-based Contrast Agent Modeled on Equation of Hirano and Suzuki[9]



A, Fast elimination of gadolinium-based contrast agents (practically universally) mirrors that of glomerular filtration rate (as most are entirely or largely eliminated by the kidney, similar to inulin); B, Intermediate- and long-term elimination of gadolinium after magnetic resonance imaging contrast exposure. Pictured are the results reported by patient advocates Hubb Grimm and Sharon Williams (gadoliniumtoxicity.com).[11] The 24-h urine results were transformed to the natural log to calculate the rate constants, assuming that the intermediate elimination was < 20 mo and slow elimination > 20 mo. By linear regression, the former (n = 33), $r^2 = 0.58$, $P < .001$ and the latter ($n = 16$), $r^2 = 0.11$, $P = .18$.

The science concerning the mechanisms of how Gd exerts its pathologic effects is lagging behind the commercialization of enhancing Gd elimination (ie, chelation therapies) and other untested remedies. Practitioners need to acknowledge the unknown potential consequences of Gd and listen to patients who suspect chronic adverse effects.

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Ethics and consent

Verbal informed consent was obtained from the patient; patient identifiers were removed to protect the patient's identity.

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