GadoliniumToxicity.com
(Coming Spring 2013)

Overview of Gadolinium Toxicity from MRIs with Contrast

The information presented comes from extensive research of published medical and scientific literature. We believe the published facts indicate that potentially all patients, and not just those with severe renal impairment, are at risk of developing varying degrees of Gadolinium Toxicity as a result of contrast-enhanced MRIs and MRAs. We are not medical professionals, and nothing stated in the Overview should be taken as medical advice.

Team of Patient Advocates
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Overview of Gadolinium Toxicity from MRIs with Contrast

If patients have had an MRI or MRA with contrast and they are presenting with unexplained or worsening symptoms, their health problems might be the result of Gadolinium Toxicity.

What is Gadolinium?

- It is a Rare Earth Element (REE); it is atomic number 64 on the Periodic Table and its symbol is Gd.[1,2]
- Gd is a lanthanide. Lanthanides are referred to as "bone seekers" because they tend to deposit in bone.[3]
- Gadolinium is a metal with strong paramagnetic properties. It has no known biological use in the human body.
- The free Gadolinium ion (Gd^{3+}) is toxic.[4,5,6,7,8,9,10]

Gadolinium-Based Contrast Agents are used for MRI and MRA.

- In the early 1980s contrast agent developers determined that Gadolinium's paramagnetic properties could be used to enhance images of abnormal tissue on MRI and MRA.[11,12]
- Since free Gadolinium is toxic, the Gadolinium ion must first be chelated or bound to a ligand.[13] The resulting complex is a Gadolinium-Based Contrast Agent (GBCA) which is injected intravenously during an MRI/MRA.
- The injected GBCA should clear the body via the kidneys before the toxic Gd ion can separate from the ligand.[14]
- There are several factors known to increase the risk of the GBCA separating while still in the body, including impaired kidney function, transient acute kidney injury (AKI), acidosis, and transmetallation.[14,15,16,17,18,19,20]
- It's believed that, other than kidney impairment, transmetallation poses the greatest potential risk for the release of the toxic metal ion from the chelate.[21,22] Transmetallation is a potential risk for *every* patient.

A problem became evident in 1997.

The first Gadolinium-Based Contrast Agent, Gd-DTPA also known as Magnevist, was approved in 1988. Although it wasn't known at the time, evidence of a problem related to GBCAs first appeared in 1997 when a new fibrosing skin disorder was seen in a group of dialysis patients.[23] The disease was later named Nephrogenic Fibrosing Dermopathy (NFD). Further evaluation, including autopsies on deceased NFD patients, found that the damage went far beyond the skin. The name was then changed to Nephrogenic Systemic Fibrosis (NSF).[24] In 2006 the connection was first made between GBCAs administered for MRI and the disease currently known as NSF.[25,26]

NSF – It's not caused by the kidneys.

Dr. Jonathan Kay, Director of Clinical Trials at Massachusetts General Hospital, suggested the disease be called Gadolinium-Associated Systemic Fibrosis or GASF, since as he said, "NSF neither originates in the kidney nor is caused by factors originating in the kidney".[27] It's the Gadolinium in tissue that seems to drive the fibrosis.[28]

- Studies have shown that all GBCAs and Gadolinium Chloride ($GdCl^{3+}$) stimulate fibroblast proliferation in tissue taken from *healthy* subjects.[29,30,31] (Fibroblasts play a role in the production of connective tissue and fibrosis.)
- There is a growing body of research that provides evidence of Gadolinium or its toxic effects also being found in bone and tissue of study animals and humans with *normal renal (kidney) function.*[32,33,34,35,36,37,38,39,40,41]
- Based on that research, it seems logical to believe that patients with "normal" renal function (meaning eGFR>60) might also be at risk from injected Gadolinium-Based Contrast Agents.

Retained Gadolinium poses a risk for all patients.

The dangers of contrast for patients with severely impaired kidney function are well known, but it's believed that contrast-enhanced MRIs and MRAs are safe for everyone else. However, published research indicates that some free Gadolinium from *every* standard dose of contrast may remain in the body, even in patients with normal kidney function.[11,42,43,44] What if patients received 5, 10, 20 or more doses or perhaps "off-label" double or triple doses that are often used for MRA? How much retained Gadolinium can the human body tolerate?

Patients exposed to Gadolinium show symptoms of heavy metal toxicity/poisoning.

From our own interactions with other affected patients with normal kidney function, we know that those exposed to GBCAs experience a new onset of many unexplained and often worsening symptoms that are consistent with those associated with poisoning from other metals such as mercury, lead and aluminum (see list below).[45,46,47,48] These patients have had numerous tests that have ruled out other diseases as the cause. The one thing that they have in common is their exposure to Gadolinium, which is known to adversely affect all body systems.

Symptoms of metal toxicity include: Short-term memory loss - decreased cognitive function - depression headaches - sleep disorders - chronic fatigue - drowsiness or grogginess - sinusitis - allergic reactions - Candida muscle spasms & weakness - muscle & joint pain - poor bone density - burning extremities - numbness & tingling peripheral neuropathy - inflammation of mouth & gums - burning tongue - metallic taste - gastrointestinal issues carpal tunnel - pressure, ringing or popping in ears - hearing loss - dizziness & loss of balance - rashes & itchy skin dry skin - difficulty swallowing - reflux - dry mouth - hoarseness - thyroid dysfunction - kidney or liver damage cold hands & feet - low body temperature - high or low blood pressure - pain in heart region/angina - MS (new) progressive vision loss - electrifying feeling/vibration within the body

Evidence of Gadolinium in patients with normal kidney function exists.

Even though studies show that GBCAs affect the blood and tissue of those with *normal* renal function,[31,49,50] patients with normal kidneys are not being evaluated for the effects of Gadolinium Toxicity. There is verifiable evidence that Gadolinium is being retained in these patients.

- Patients with normal kidney function are excreting levels of Gadolinium that are well above Mayo Laboratories Reference Range (>0.4 mcg) as long as several years after their last contrast-enhanced MRI or MRA.*
- Provoked urine tests found high levels of Gadolinium, confirming that it was deposited in the patient's body.* (Provoked tests use a chelating agent to stimulate the release of deposited Gd prior to a 24-hour urine collection.)
- No Gadolinium should be detected if the GBCA had been excreted before the ligand and Gd ion separated.
- Mayo Clinic's urine and blood tests for Gadolinium note that "because the ionic radius of Gadolinium (3+) is similar to that of Calcium (2+), it may also deposit in bone".[51,52] Gd was found in hip bone removed from a patient 8 years after her last contrast MRI, confirming that Gd deposits in bone where it can remain for years.[42]
- Diagnostic criteria are needed to evaluate ALL patients for evidence of Gadolinium Toxicity.

* Non-published urine test results obtained from multiple patients with eGFRs >60.

Important facts about Gadolinium to consider before ordering, or having, contrast MRIs.

1. Each single standard dose of a GBCA contains approximately 1.5 grams of Gadolinium, of which **approximately 1% (15 mg) may be retained in the body** even in patients with normal renal function.[43,44]
2. A 2008 study indicates deposited Gadolinium may be mobilized over time from bone stores.[53]
3. Gd affects more than the skin. Autopsies found extensive multiorgan fibrosis and calcification, as well as vascular and extracellular deposits of Gd.[54] Areas affected include: liver, lungs, heart, kidneys, thyroid, diaphragm, blood vessels, entire GI tract, eyes, brain, spinal cord, and connective tissue.[55,56,57,58,59,60,61,62]
4. Gadolinium-Based Contrast Agents have been found to be nephrotoxic.[63,64,65]
5. Gadolinium is neurotoxic.[66,67,68] It also inhibits mitochondrial function and induces oxidative stress.[69,70]
6. GBCAs should not cross an *intact* Blood-Brain Barrier (BBB); however, there are many ways that BBB permeability might be increased or temporarily altered, including by MRI itself.[71,72,73,74,75,76,77,78,79,80,81,82,83,84,85]
7. Gd deposits and *accumulates* in tumors and lesions, regardless of the patient's level of renal function.[12,40,41]
8. Studies show one agent caused more skin lesions while all were found to deposit in bone and tissue.[86,87,88,89]
9. A GBCA was found to promote Multiple Myeloma cell growth.[40]
10. MS patients had worsening symptoms after contrast MRIs.[90,91] Hyperintense lesions lead to brain atrophy.[92,93]
11. Since at least 1991, it has been known that some Gadolinium would remain in the body of all patients and it could result in a toxic effect.[22] The long-term effects of deposited Gadolinium are still unknown.[94,95]
12. ALL GBCAs can cause NSF/GASF; there are even cases linked to the more stable macrocyclic agents.[96]

The key points related to Gadolinium.

1. No studies have been done to determine how much Gadolinium is retained in patients with normal kidneys.
2. No studies have been done to evaluate the effects of cumulative doses from multiple contrast MRIs and MRAs.
3. No studies have been done to determine the long-term effects of deposited Gadolinium in all patients.
4. Most patients are unaware of the potential adverse effects that Gadolinium can have on their bodies.
5. Most doctors do not know that Gadolinium could be deposited in all patients who have contrast MRIs/MRAs.
6. Patients are told GBCAs pose risks only for the renally-impaired; published literature suggests otherwise.
7. After exposure to GBCAs, some patients with normal kidney function show signs of heavy metal poisoning.
8. There are no known methods to safely remove retained Gadolinium from the body.
9. NSF/GASF is a debilitating and potentially life-threatening disease, and currently there is no cure.

Is history repeating itself?

Thorotrast was a radiocontrast agent used from 1930 to 1960. It wasn't until the late 1940's that the first "Thorotrast-related malignancies" were described and the problem came to light. Thorotrast had such a long-latency period that malignancies might not show up for 45 years or more later.[97] On autopsies of NSF patients, Gadolinium and/or the fibrosis it caused has been found in many of the same areas where Thorotrast deposited, plus more.[98,99,100] *Could Gadolinium-Based Contrast Agents be the next Thorotrast?*

Up until now, patients with normal renal function have been overlooked.

It appears that a determination as to whether or not a patient has been adversely affected by Gadolinium is based primarily on two things: renal impairment and presentation of skin changes consistent with the current diagnostic criteria for NSF. However, even among renally-impaired patients, skin findings are *not* uniform.[101,102,103,104,105,106]

- If there are differences seen among renally-impaired patients, might there also be differences seen between the renally-impaired and non-renally-impaired?
- NSF has presented as a progressive myopathy or muscular disease, with minimal skin findings, in a patient in acute renal failure.[107] Isn't it possible that when less Gadolinium remains in the body, such as might happen to someone with normal kidney function, that it might also result in different skin findings or possibly few if any visible skin changes at all?
- Based on autopsy findings in NSF patients, isn't it also possible that damage is occurring on the *inside* of the patient and not readily seen with the naked eye, regardless of the patient's level of renal function?

While there appear to be many unanswered questions related to Gadolinium-Based Contrast Agents, what is known from the literature is that Gadolinium is toxic to humans and varying amounts of it have been detected in bone and tissue of patients – including in patients *without* severe renal disease. It seems that these facts alone should be sufficient to allow for a Gadolinium-related diagnosis for all patients affected by their exposure(s) to GBCAs.

What you can do.

Based on the facts from published literature, it seems contrast-enhanced MRIs/MRAs should be ordered cautiously. We hope you will remember the facts presented here and openly discuss all the risks with your patients beforehand. When patients present with unexplained or worsening symptoms, including those patients with normal renal function, please consider their prior exposures to Gadolinium-Based Contrast Agents. Until all patients exposed to GBCAs are evaluated, we won't know the full extent of damage being caused by Gadolinium.

Please report any suspicions of a possible link to Gadolinium-Based Contrast Agents to the FDA immediately by filing a MedWatch Adverse Event Report. Call 1-800-FDA-1088 or report via the MedWatch website at http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

If you live outside the U.S., please report to your country's equivalent governing agency.

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