

August 23, 2017

Docket No. FDA-2017-N-1957

Medical Imaging Drugs Advisory Committee; Notice of Meeting; Request for Comments

Submitted by Sharon Williams and Hubbs Grimm, coauthors of The Lighthouse Project at GadoliniumToxicity.com.

We want to thank the FDA and members of the Medical Imaging Drugs Advisory Committee for giving us the opportunity to provide input to the Committee and to speak during the Open Public Hearing portion of the September 8, 2017 meeting regarding gadolinium retention from gadolinium-based contrast agents (GBCAs) administered for contrast-enhanced MRIs. While we both have been adversely affected by retained gadolinium, and have proof of long-term retention, that is not the most important content that we present to the Advisory Committee.

Who we are -

In 2012, after two-years of researching peer-reviewed publications, Sharon became convinced that gadolinium from contrast MRIs was the cause of her otherwise unexplained symptoms and it prompted her to write to the FDA about facts from the published literature that supported her concerns. Upon discovering others were in a similar situation, she was one of the leaders who started the internet-based MRI-Gadolinium-Toxicity Support Group which currently has more than 330 members from around the world, with most being in the USA. Sharon has had personal contact with each member, all of whom appear to be suffering clinical implications of gadolinium retention from contrast-enhanced MRIs. It is important to note, that there are other online gadolinium-related patient advocacy groups, but we are providing evidence from only the Yahoo-based MRI-Gadolinium-Toxicity Support Group.

In 2014, Sharon partnered with Hubbs to start The Lighthouse Project website at GadoliniumToxicity.com to shed light on the effects of retained gadolinium from contrast MRI. Our site has become an important source for information on this topic, and has been referenced by several recently published papers. The Lighthouse Project has gained considerable respect for its fair and fact-based treatment of the issue of gadolinium retention, and radiologists and other medical professionals have referred patients to our website and to us personally. We have published three original research papers on our site that are based on the information gathered from people in the Gadolinium Toxicity Support Group. These papers document both the symptoms of gadolinium toxicity and evidence of long-term gadolinium retention in this group of individuals. Our latest paper, "Gadolinium Retention from Contrast MRIs in 70 Cases with Normal Renal Function – 24-hour Urine Test Results" provides the most comprehensive look so far into this evidence of gadolinium retention. Important data from that paper and as yet unpublished related information are provided below.

Together we provide a significant storehouse of information on the effects of retained Gadolinium from contrast MRIs. Sharon has communicated directly with nearly 400 people and knows their personal stories. Hubbs has analyzed over 300 urine test results and helped over 125 people to understand how their results compare with others in similar situations. We solicit your receptiveness to consider the information we provide.

Sharon's 2012 letter to the FDA, and our 2014 Symptom Survey and 2017 Gadolinium Retention paper are also submitted as part of our Comments. Even though Sharon's letter to the FDA was written 5 years ago, it contains

relevant facts from the published medical literature about Nephrogenic Systemic Fibrosis (NSF) and the toxic effects of gadolinium, and it addresses some important questions that we still don't have answers to.

Our Case for Why the FDA Needs to Take Action

From our personal experience, our extensive research of the medical literature, and our work with more than 330 people who developed unexplained symptoms after MRIs with contrast, we make the case that the FDA needs to take action in a timely manner regarding the use of Gadolinium-Based Contrast Agents and the dissemination of information about gadolinium retention to clinical practitioners and patients. We provide evidence related to the following 6 points:

1. **Medical literature** documents toxicity of gadolinium and systemic implications.
2. **The Risk Factors** for adverse results are many.
3. **NSF-Like Symptoms** in patients with normal renal function.
4. **Gadolinium from GBCAs does not clear the body in a few days**, or even in a few months, allowing plenty of time for the Gd ion to dissociate from the chelate.
5. **Underreported Symptoms** from Contrast MRIs is a serious problem.
6. **There is evidence of clinical implications of gadolinium deposition.**

Medical literature documents toxicity of gadolinium and systemic implications

The toxicity and systemic implications of retained gadolinium have been known since well before the December 2013 paper by Kanda et al. that reported signal hyperintensities in the brain which we now know are the result of gadolinium deposition. When we first started to research NSF, it didn't take long to realize that things just didn't add up. The studies published by mid-2012 show that all patients are at risk of retaining gadolinium and not just those with severe renal disease. However, that was the opposite of what the NSF-related literature said. Realizing that gadolinium retention was a much bigger problem than many believed, Sharon wrote to the FDA in October of 2012 and shared the facts she had discovered since early 2010. Because of the potential for the Gd ion to be released from the chelate in vivo and the risk factors documented in the next section, the following substantiate the possibility of related symptoms of gadolinium toxicity in people with normal renal function.

Gadolinium competes with Calcium in all biological systems

Gadolinium (Gd³⁺) has an ionic radius similar to that of Calcium (Ca²⁺) which is why Gd³⁺ is so toxic in biological systems – Gd³⁺ can compete with Ca²⁺ in all biological systems that require Ca²⁺ for proper function and, in doing so, the trivalent Gd³⁺ ion binds with much higher affinity. (2009, Sherry et al.)

Gadolinium (III) Chloride is toxic to mammals and has no biological use in the human body

(1961, Haley et al.); (1966, Gabbiani et al.); (1996, Hirano et al.); (1997, Spencer et al.); (1997, Rees et al.); (2006, Adding et al.)

Gadolinium is neurotoxic

(1991, Roman-Goldstein et al.); (1996, Ray et al.); (1998, Ray et al.); (2011, Feng et al.)

Gadolinium inhibits mitochondrial function and induces oxidative stress

(2010, Feng et al.); (2011, Xia et al.)

Gadolinium-induced oxidative stress triggers endoplasmic reticulum stress in rat cortical neurons

(2011, Xia et al.)

Gadolinium increases vascular reactivity

(2011, Angeli et al.); (2011, Vassallo et al.)

Gadolinium Chloride induced Kupffer-cell phagocytosis blockade

(1980, Husztik et al.)

Gadolinium induces macrophage apoptosis

(1996, Mizgerd et al.)

Brain bio-electric changes have been detected after IV administration of gadolinium-based contrast

(2001, Salvolini et al.); (2005, Messori et al.)

GBCAs can be nephrotoxic

(2006, Akgun et al.); (2006, Elmstahl et al.); (2007, Heinrich et al.); (2007, Penfield et al.)

Gadolinium-containing contrast agent promoted Multiple Myeloma (MM) cell growth

(2009, Fulciniti et al.)

Evidence that gadolinium affects blood and tissue of those with normal renal function

(2008, Edward et al.); (2009, Varani et al.); (2009, Wermuth et al.); (2010, Bhagavathula et al.); (2010, DaSilva et al.); (2010, Edward et al.); (2010, Del Gado et al.); (2012, Bleavins et al.)

Gd deposition in patients with normal or near normal renal function was reported before 2012

(2004, Gibby et al.); (2009, Darrah et al.); (2010, Xia et al.); (2011, Christensen et al.)

Delayed & hyperintense enhancement of Cerebrospinal Fluid (CSF) in patients w/normal renal function

(1997, Naul et al.); (2000, Mamourian et al.); (2007, Morris et al.); (2007, Levy); (2008, Hamilton et al.)

Gd retention in the brain documented before 1996 in two patients with Erdheim-Chester Disease

(1989, Tien et al.); (1995, Martinez)

GBCAs effect thyroid hormone receptor action and thyroid hormone-induced cerebellar Purkinje cell morphogenesis

(2016, Ariyani et al.)

The literature clearly indicates that retained gadolinium can adversely impact the human body and affect multiple body systems. The 2016 study by Ariyani et al. makes it clear that there is still much more to learn about the toxic effects of gadolinium.

Risk factors for gadolinium retention are not unique to the renally-impaired

The primary risk factor for gadolinium retention and the development of NSF is having severely impaired renal function, meaning having an estimated glomerular filtration rate (eGFR) below 30. NSF is a potentially fatal disease that has been diagnosed almost exclusively in patients with end-stage renal disease (ESRD). Prolonged excretion times and the instability of the GBCA results in the toxic gadolinium ion separating from the ligand and remaining in the body. However, impaired renal function is not the only risk factor that patients face when they have a contrast-enhanced MRI. Most risk factors have the potential to affect everyone who undergoes an MRI with contrast. Recent studies confirm gadolinium deposition in people with normal renal function.

Risk factors that could result in gadolinium retention in any patient exposed to a GBCA include –

Stability of the agent used, cumulative dosage, and high dosages – This is well-documented.

Acidosis – This is a condition in which the body has more acid than normal. This can cause the pH of the blood and body tissues to fall below the healthy range of 7.35-7.45. The rate of gadolinium release increases with decreasing pH. (2009, Aime et al.) Some of the causes of acidosis include: high protein diets, excess coffee and alcohol consumption, chronic disease, toxic exposure, certain medications, prolonged vigorous exercise, diabetes, cancer, dehydration, low blood sugar, poor digestion, the normal process of aging, liver failure, and kidney disease. (2004, McNaughton)

Acute Kidney Injury (AKI) – This is a common clinical problem and often occurs in the elderly and during hospitalizations and after surgeries. (2009, Soni et al.)

Extravasation – This occurs when the GBCA is accidentally injected into the surrounding soft tissue instead of directly into the vein. (2007, Ersoy et al.)

Proinflammatory Event – This could be a recent surgery, infection, vascular procedure, or thrombosis near the time of a contrast-enhanced MRI. (2007, Sadowski et al.)

Transmetallation – This is the displacement of the gadolinium ion from the chelate by other metal ions in the body such as zinc, calcium, copper, and iron. The metals can work at the same time to destabilize the GBCA complex which can result in more Gd remaining in the body. Other than renal impairment, researchers have said that transmetallation presents the greatest potential risk for the release of the toxic metal ion from the chelate. (1990, Cacheris et al.); (1991, Rocklage et al.)

Since at least 1992, dechelation or separation of the ion and ligand due to transmetallation and acid dissociation was confirmed in animal studies. (1992, Kasokat & Urich); (2006, Idée et al.)

Transmetallation has occurred in people with normal renal function. (1996, Puttagunta et al.); (2005, Kimura et al.); (2010, Greenberg)

Altered Blood-Brain Barrier – A risk factor that seemed to be somewhat overlooked until recently is having a compromised blood-brain barrier (BBB). The presence of a tumor or lesion, or anything that alters the BBB can result in gadolinium being deposited in brain tissue regardless of the patient's level of renal function. All GBCA Product Labeling indicates that Gadolinium-based Contrast Agents "do not cross an intact blood-brain barrier"; however, "disruption of the blood-brain barrier" or "abnormal vascularity" allows accumulation in lesion such as neoplasms (tumors), abscesses, and subacute infarcts.

Since at least 1984, it has been known that "Gadolinium-DTPA does accumulate at sites of blood-brain barrier disruption with obvious enhancement of central nervous system lesions including tumors and abscesses".

(1984, Brasch, Inherent contrast in magnetic resonance imaging and the potential for contrast enhancement. The 1984 L. Henry Garland lecture). The word “accumulate” in Dr. Brasch’s presentation caused Sharon to broaden her areas of research and look for other ways gadolinium might get into the brain and she discovered that there are many.

The literature indicates that BBB permeability can be increased or temporarily altered including by MRI itself. (1987, Shivers et al.); (1990, Prato et al.); (1994, Prato et al.).

Some of the other ways the literature indicates the BBB can be crossed or altered include:

- having Type II Diabetes or a white matter hypersensitivity like hypertension (2003, Starr et al.)
- lack of a BBB on the Optic Nerve Head (1975, Tso et al.); 2001, Hofman et al.)
- lack of BBB on Circumventricular Organs (CVOs) (2009, Maalood et al.)
- lack of BBB on Choroid Plexuses (2006, Yokel et al.); (2001, Engelhardt et al.)
- diffusion into the vitreous and aqueous humors of the ocular globes, perivascular spaces, and ventricles of the brain (2002, Kanamalla et al.)
- diffusion into subarachnoid space (2000, Mamourian et al.); (2001, Boyko et al.)
- diffusion into subdural spaces (2001, Kanamalla et al.)
- effects of Electromagnetic Pulse (EMP) (2009, Qui et al.); (2010, Ding et al.)
- effects of Electromagnetic Fields (EMFs) (2008, Salford et al.); (2009, Nittby et al.)
- effects of RadioFrequency (RF) fields (2008, Nittby et al.)

As you can see, all but one of the known risk factors that might cause someone to retain gadolinium could impact almost any patient at any given time. They are not unique to patients with severe renal disease. Of most concern are the various ways that gadolinium might enter the brain. Because patients with brain pathology will almost certainly have gadolinium deposited in their brain, it is critically important to determine the long-term consequences of that deposition.

NSF-like symptoms in patients with normal renal function should be expected based on published findings associated with NSF

Retained gadolinium affects far more than the skin. What was first thought to be a new skin disorder was instead a systemic disease that can affect all body systems with devastating effects. Autopsies of deceased NSF patients have found extensive multiorgan fibrosis and calcification, as well as vascular and extracellular deposits of gadolinium.

Although recent studies have said that they see no evidence that gadolinium deposited in the brain and elsewhere in the body causes any clinical symptoms or harm, facts from published literature, including autopsy reports of deceased NSF patients, indicate that may not be the case. The symptoms reported by the patients we know indicate that they also have a systemic disease process going on, but perhaps not as severe or aggressive as that experienced by severely renally-impaired patients with NSF.

Gadolinium Toxicity – a Disease of Degrees

Gadolinium Toxicity is a “Disease of Degrees” with NSF likely being the worst manifestation of it, but there is no reason to think it will be the only disease process associated with retained gadolinium since any amount of gadolinium would still be toxic and could cause adverse effects to varying degrees. It makes no sense to us to think that retained gadolinium will cause full-blown NSF or nothing at all.

In early 2014, we released the results of a Symptom Survey which, to the best of our knowledge, was the first to report on the symptoms associated with Gadolinium Toxicity in patients with normal renal function. A 2016 study by Semelka et al. reported similar symptoms and they determined that “many of the respondents reported signs and symptoms that are consistent among subjects, and include various findings similar, but less severe than found in NSF”. Hence, a “disease of degrees”.

There are degrees of severity even in NSF.

Since NSF was first described in the literature, most papers have focused on the skin manifestations of the disease as it was first seen in severely renally-impaired patients, most of whom were on dialysis. However, even among renally-impaired patients, skin findings are not uniform.

NSF has presented as a progressive myopathy or muscle disease, with minimal skin findings. (2010, Edgar et al.) It has been reported that the skin manifestations in the late stages of NSF are different from those seen early in the disease and have a varied presentation. (2006, Boyd et al.); (2008, Girardi); (2009, Bangsgaard et al.)

Matsumoto et al. (2012) suggested the occurrence of a non-plaque, late-onset type of NSF in patients who presented clinically with glossy, smooth skin with gradual hardening of the skin. That group’s symptoms were reported to develop longer after their last exposure to gadolinium. The authors suggested that the “late-onset of NSF may be explained by the slow release of free gadolinium from bone stores”. Since bone appears to be the primary storage site of retained gadolinium, even people with normal renal function will have gadolinium in their bones that will be released back into circulation over time. A 2004 study by Gibby et al. confirmed Gd deposition in bone within a few days after contrast administration in people with normal renal function; this occurred with both a linear and macrocyclic agent.

Symptoms of NSF patients –

When we did our 2014 Symptom Survey paper, we could not find a comprehensive catalogue of NSF patient symptoms. However, articles regarding NSF describe both symptoms and affected body systems that are similar

to those reported in our paper. The following symptoms of NSF are detailed on the official website of the International Center for Nephrogenic Systemic Fibrosis Research (ICNSFR).

Cowper SE [ICNSFR Website on March 13, 2014] reports symptoms and signs of NSF that include swelling and tightening of skin, joint contractures, and skin changes described as reddened or darkened patches, papules, or plaques. Skin may feel “woody” and resemble the texture of the peel of an orange. There may be burning, itching, or severe sharp pains in involved areas. Muscle weakness often occurs. Radiography may reveal calcification of the soft tissue. Deep “bone pain” has been described in the hips and ribs. Hand and foot swelling with blister-like lesions has been reported. Some patients have yellow papules or plaques on or near the eyes. Rapid, new onset fluctuating hypertension of unknown cause has been described prior to onset of the skin lesions.

Most of what is known about the systemic nature of NSF has been learned from autopsy case studies of deceased patients. We will not review them all, but we want to highlight three studies here due to the scope of the authors’ findings and how the body systems affected link to our 2014 Symptom Survey.

Swaminathan et al. (2008) reported unique cardiac and vascular events in NSF including sudden monocular blindness secondary to posterior ischemic optic neuropathy, limb ischemia, and recurrent cardiac arrhythmias. They presented the first evidence that NSF is associated with systemic deposition of metals including gadolinium, iron, and aluminum, with the highest quantity of gadolinium deposited in the heart, blood vessels, and skin.

Sanyal et al. (2011) conducted an autopsy-based review of one NSF case along with a review of published literature. Insoluble Gd-phosphate deposits were detected in the skin, liver, lungs, intestinal wall, kidney, lymph node, skeletal muscle, dura mater and cerebellum of the NSF autopsy case, primarily in vascular walls. The authors believed this to be the first case to document Gadolinium deposition in brain parenchyma in NSF. They noted that apart from diagnostic findings in skin, fibrosis of muscle and dura may be more prominent in NSF patients.

Zou and Ma (2011) reviewed 408 biopsy-confirmed cases of NSF. Clinical features noted include: dermal pain, thickening and hardening, especially in lower extremities; sharp pains, burning or itching in affected areas; joint contractures or limited range of motion; “stiffness” without contractures; scleral plaque or injection. Over one-third of patients were without contractures or limited range of motion; the authors felt this suggests that these patients had a mild form of NSF. (Perhaps NSF is the “disease of degrees”).

To show how these toxicities have impact, we present Sharon’s experience

I have had 5 doses of Magnevist with a cumulative dosage of 90 cc. I had dose 1 in mid-2000, doses 2 and 3 in 2008, and doses 4 and 5 within six-weeks of each other in early 2010.

After my first dose of contrast in 2000, I began to have mild localized head pain on the top left-side of my head that was always in the same spot and I also developed GI issues. At the time, I didn’t associate it with my MRI. The intensity of my head pain slowly increased over time. By late 2007, the pain became more frequent and intense. As the pain intensified, more MRIs with contrast were ordered and my symptoms got worse after each one. After an unenhanced brain MRA in late 2009, the pain in my head became dramatically worse, my blood pressure shot up, my body temperature dropped, I had intense electric-like sensations in my legs, muscle spasms and more. That led to my last two MRIs with contrast within 6-weeks of each other in early 2010. Since an unenhanced brain MRI on March 19, 2012, my brain feels like it has been cut in half right down the middle – frequent pain on the left-side and 24/7 pressure on the right-side. No tumors or lesions have ever been detected.

I finally made the connection between my worsening symptoms and my MRIs with contrast in March of 2010 after my last two MRIs. Before my 4th dose of contrast, I was told I had to have my kidney function checked because I had turned 60 and had hypertension. I did a quick search online and everything I read said that “GBCAs are safe as long as you don’t have severe renal disease”. My eGFR then and now is greater than 60 so the MRI Tech told me “you don’t have anything to worry about because your number is over 30”. Little did I know how wrong he was, but I don’t fault him because he didn’t know any better especially not in 2010. If I knew then what I know now about GBCAs and the toxic effects of gadolinium, I would not have had my last two doses of contrast.

My case addresses symptoms and how they can be linked to what we know about NSF and the toxic effects of gadolinium. I have confirmation of long-term gadolinium retention from both urine tests and the testing of my thyroid tissue which was removed 51 months after my last dose of Magnevist. Thomas Darrah, PhD, co-author of the frequently referenced 2009 paper “Incorporation of excess gadolinium into human bone from medical contrast agents”, tested the tissue and reported that, “based on the simultaneous analysis of other rare earth elements, it is clear that this does reflect Gd from a unique Gd-rich source consistent with Gd-based contrast agents”. The concentration of gadolinium in my thyroid tissue was 0.211 parts per million.

I decided to have my thyroid tissue tested after reading a 2009 paper by Koreishi et al. titled, “Nephrogenic Systemic Fibrosis – A Pathologic Study of Autopsy Cases”. Case 2 described extensive systemic fibrosis that involved not only the patient’s thyroid gland, but also pericardium, heart, lungs, diaphragm, and dura mater, including that surrounding the spinal cord. This was the first report of fibrosis of the thyroid in NSF that manifested clinically as hypothyroidism. I now have Hashimoto’s thyroiditis, constant pain and pressure inside my head, neck and back pain, burning pain in my lower legs and hands, swallowing problems, GI issues, bone pain, thickened tissue, very dry eyes and progressively worsening vision, and other ongoing symptoms.

Quite a few people in our MRI-Gadolinium-Toxicity support group have developed hypothyroidism and Hashimoto’s thyroiditis since their MRIs with contrast as well. A 2016 study by Ariyani et al. might explain some of our symptoms that are related to thyroid function. The title of the paper is “Effects of Gadolinium-Based Contrast Agents on Thyroid Hormone Receptor Action and Thyroid Hormone-Induced Cerebellar Purkinje Cell Morphogenesis”. The connection between GBCAs, gadolinium, and the thyroid gland requires further investigation as soon as possible.

We know from the NSF literature and Sharon’s case that gadolinium deposits in the thyroid gland and various other tissues in the body. It causes a range of clinical symptoms, but what we still do not know, is how much gadolinium the human body can tolerate before long-term damage is done.

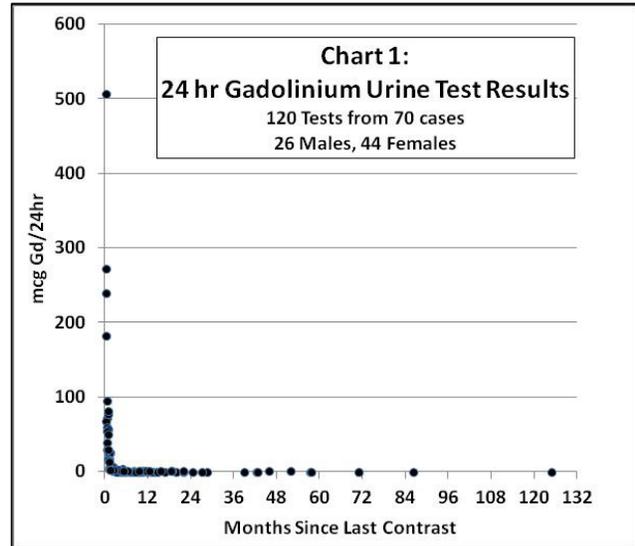
Gadolinium from GBAs does not clear the body in a few days, or even in a few months

Hubbs: *I had no reason to question the MRI technicians when they said that the contrast used for my 9 MRIs would be out of my body in a few days. But when a futile search with traditional doctors could not explain my muscle vibrations and growing numbness and burning pain in my feet, I was referred to a wellness doctor by a psychiatrist. In August 2010, 10 months after my last contrast MRI, his routine 24hr urine test turned up an excessive amount of gadolinium, an element I had never even heard of. I have since tracked it about every 6 months, and I am still excreting gadolinium today, nearly 9 years after my last contrast MRI. Each day, about 0.5 mcg Gd is excreted. After 6 years, my results were still above the Mayo reference range that is supposed to be valid 4 days after a contrast MRI. If I do chelation, that result jumps up to around 14.0 mcg Gd/24hr, so there is plenty still in my body.*

When I joined the MRI-Gadolinium-Toxicity Support Group, I found others who had similar symptoms and urine tests for Gadolinium that they did not understand. How high is too high? How low is good? Most doctors, even the ones who ordered the test, did not have much insight into gadolinium, if any. As we compared results, I decided to keep track of the results in a database to see what we could learn.

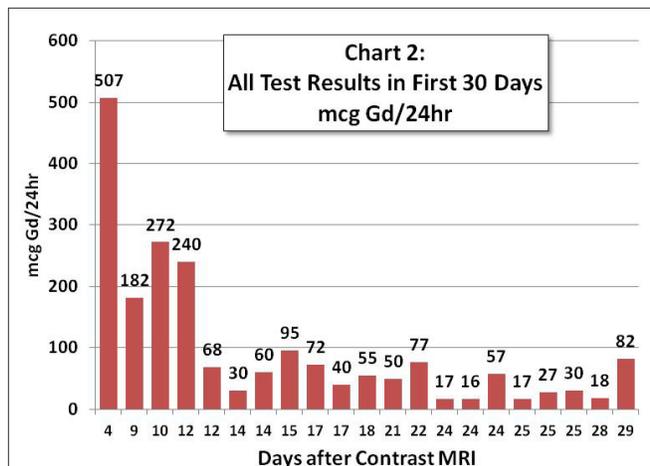
We want to share with you, our insights into 70 cases of people with similar symptoms for which we have 120 urine test results for gadolinium. We quickly figured out that everyone's results went down over time, quickly at first and much more slowly as time went on. The graph to the right shows the distribution of results in time. Notice how high some results are, as much as 500 mcg Gd/24 hours and as far out as 10 years after a contrast MRI.

Looking closer, we will demonstrate, at least for these people, gadolinium from contrast MRIs does not clear the body in a few days, a few months, or even many years.



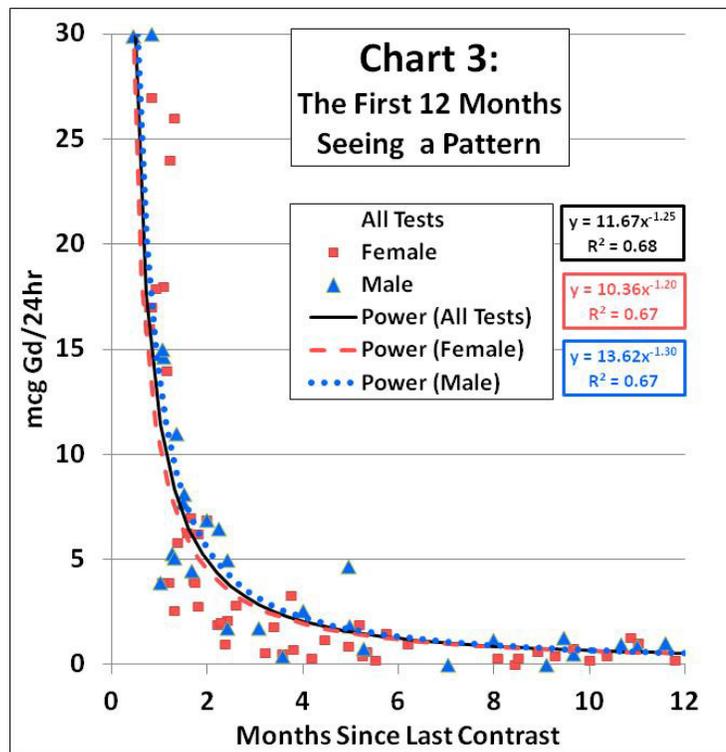
Results in the First 30 Days After a Contrast

The chart to the right shows all of the tests that people have done in the first 30 days (it is rare for people to discover the gadolinium connection and have their urine tested in this time frame). Note how high the results are for the first four cases - for as long as 12 days after the contrast. None of the results for the first 30 days indicates that the gadolinium has cleared their body, or even come close to the Mayo reference range of < 0.7 mcg Gd/24hr.



The First Year - a Relationship Can be Seen

Looking at the results in the first year as shown at the right, we can see a relationship between the time since the last contrast and the gadolinium test results. The vertical axis has been truncated in order to show the detail. Separating the male and female cases, we have also shown a trend line for each of the datasets. Notice that the separate trend lines are extremely similar. The R-squared value of 0.67 or 0.68 for these trend lines indicates some level of relationship. It should be noted that this chart contains data points for all contrast agents and without regard to the number of contrast MRIs received. There is still a clear pattern.

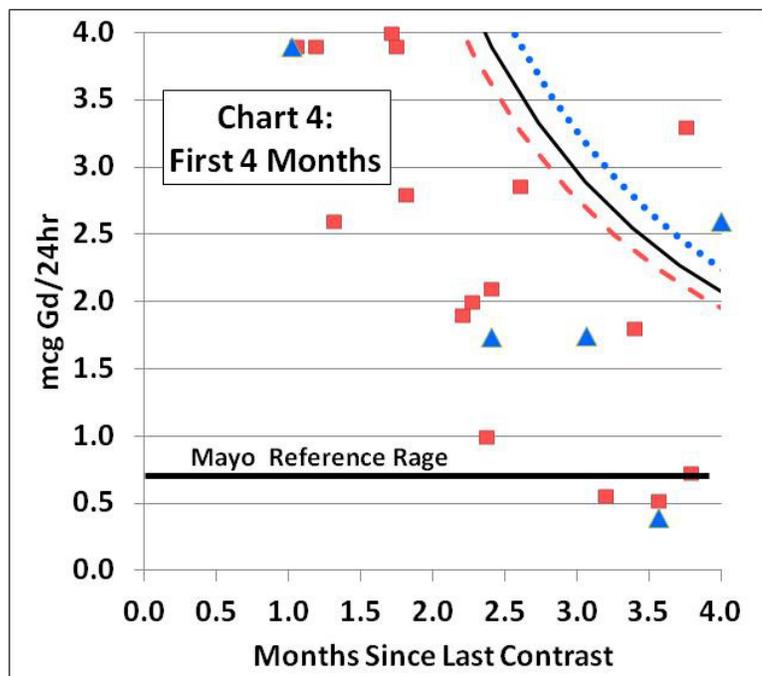


The First 4 Months - a Closer Look

This chart, showing results for just the first 4 months with a truncated vertical axis allows us to see whether there is any evidence that the gadolinium clears the body in a few days. Two features of this chart are noteworthy:

- No one got a test result of zero in the first four months which would be the case if the contrast had cleared their body.
- No one even got a result that was within the Mayo Reference Range in the first three months.

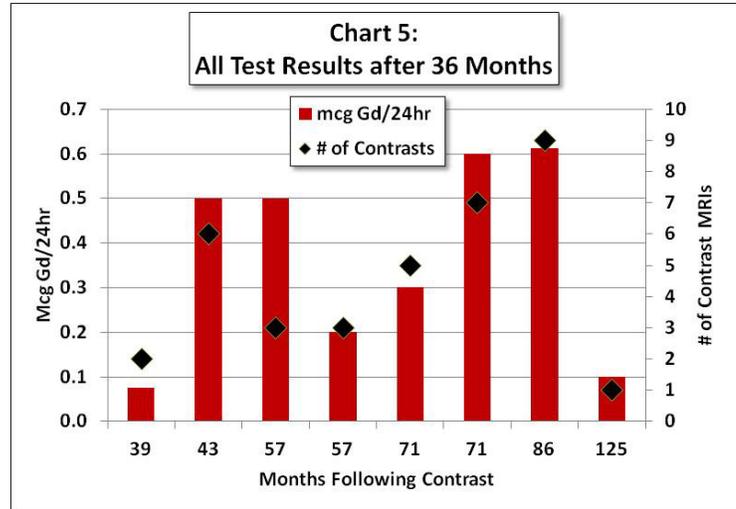
The chart covers 61 test results from 44 different people.



While we recognize that this does not have the rigor of a controlled trial run by professional medical researchers, it would be remarkable if another study found that most of the participants were free of gadolinium in a few days.

Results after 3 Years

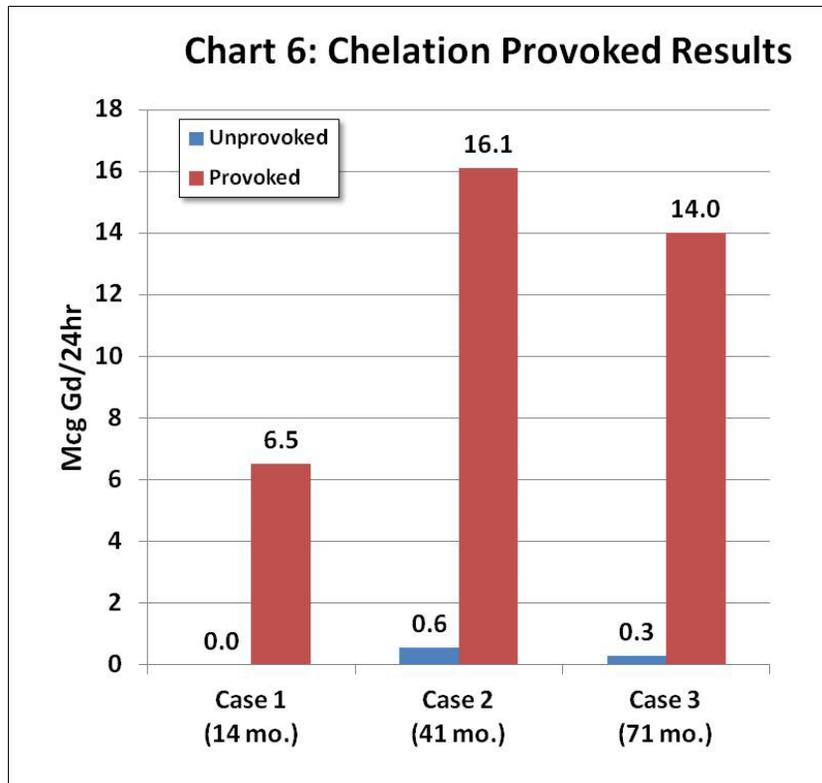
At the other end of the spectrum are the cases where people have continued to do urine testing beyond 3 years. The chart at the right shows the test results for the 8 people who did testing in this timeframe. The chart also shows, on the right axis, the number of contrasts they had received. Note the relationship between the test result and the number of contrast MRIs received, indicating a cumulative effect similar to the findings about deposition in the brain described in recent research papers.



The conclusion here is that the gadolinium is present for a much longer time than anticipated.

Evidence from Provoked Urine Testing

All of the results we have shown so far are for unprovoked urine tests, where the person did not receive any type of medication in an attempt to pull out more gadolinium from their tissues. We also have a number of provoked results, collected in the 24 hours immediately after receiving a chelating agent via IV. We have three cases where an unprovoked test was closely followed by a provoked test, and the results are shown to the right. There is a dramatic increase with provocation, even in Case 1 where the unprovoked test result was "undetectable". Note that these provoked results are similar to other cases in similar situations but for which the unprovoked test is not available. The results with multiple IV Chelations only vary marginally, not dramatically.



This demonstrates that a low unprovoked result does not indicate that there is very little gadolinium left in the body. It only indicates that there is little left in circulation and available for excretion.

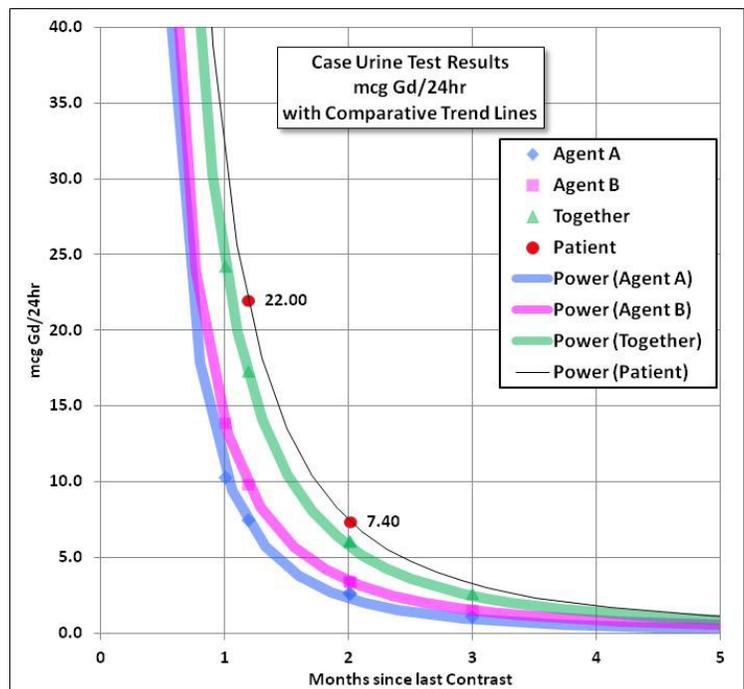
Understanding the Progression of Urine Test Results

As can be seen by the slope of the trend line in Chart 3 above, typical 24-hour unprovoked results vary significantly with time. People who have received an out-of-range result are anxious to know how their result compares with others at a similar time after their contrast. We now have enough test results from unconfounded cases in our database to build trend lines for each individual contrast agent. While we do not think it our job to get involved in the discussion of one agent compared to another, we want to show how predictable the progression of urine test results are when the trend lines are calculated from unconfounded cases. We will demonstrate this by way of a specific case.

The case we are presenting involves Agent A, a macrocyclic agent, and Agent B, a linear agent. The results we have in the database for Agent A produce a trend line with an r-squared value of 0.93, much more accurate than the trend lines shown in Chart 3. The trend line for Agent B, has an r-squared value of 0.91, also quite accurate.

The patient received Agent A for one MRI, and 10 days later received Agent B.

The chart to the right shows both of the trend lines timed from the second contrast, since that one was the last. The trend line for Agent A (blue) was time-shifted by ten days to account for the timing of the contrast MRIs. The trend line for Agent B is pink. Adding these together, we get the green trend line. There were two unprovoked tests in this case, 22 mcg Gd/24hr at 1.2 months after the last contrast, and 7.4 mcg Gd/24hr at 2.0 months. Using the same techniques, a trend line was created from the two patient test results. Notice how well the patient's trend line follows the sum of the two trend lines for the two agents received. This closeness of the patient test result to the trend line is not a unique outcome, it is the norm for the patient results we have looked at.



Here, too, we recognize that the methodology used is different from the methods that would be used in a controlled trial. However, even with the crude methods used and a relatively small database, to get a result as seemingly precise as this case indicates that the excretion patterns for each of the agents could easily be developed that would help clinicians and patients understand their test results.

Summary Regarding Clearance of Gadolinium from the Body

As we have shown, at least for these 70 cases, gadolinium did not clear the body in a few days, and for some, it is still present after nearly a decade.

Underreported Symptoms from Contrast MRIs is a Serious Problem

You are likely wondering how can anyone know that something is underreported. The answer is twofold: by hearing the stories of the 330 members of the MRI-Gadolinium-Toxicity Support Group and by personally experiencing the frustration of trying to get a doctor to consider a connection to gadolinium as a reason for unexplained symptoms. The result is the missed identification of potential links between gadolinium and serious medical conditions.

People find our website and then join the support group because they cannot get any help through their normal avenues for medical care. At a high level, their stories are most always the same:

I think I have symptoms caused by my (one or many) contrast MRIs. My doctor and the people who administered the contrast say they cannot be related because I have good kidneys. They even refuse to investigate. What can I do?

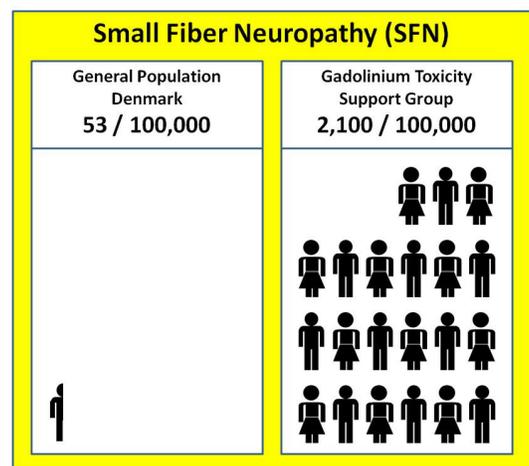
None of these medical practitioners could possibly report a connection when they believe a connection is impossible for people with normal kidney function. We do not fault these caregivers. They are acting on the information they have been given.

We will now show how this self-fulfilling belief can be a serious problem.

Hubbs: After my second contrast MRI, I experienced the feeling of electrified, vibrating muscles that most everyone has since reported in our Symptom Survey. My next 4 contrast MRIs were ordered over a period of 2 years by a neurologist to try to diagnose these feelings, and why they were continuing to get worse, spreading throughout my body. None of the other specialists at multiple institutions could offer any insights. Then, a month after having 3 more contrast MRIs in a 3-week period, my toes started to go numb, and then burning pain. More specialists, higher levels of pain, no answers. A routine urine test for toxins turned up gadolinium as significantly out-of-range. But that information offered no help to the doctors. Finally, a year later, a test for Small Fiber Neuropathy (SFN) came back positive. The ends of the nerves were dying and sending signals of burning pain. The many tests to determine the cause of SFN came back negative for all of the known causes except for metal toxicity. Even though gadolinium is known to be neurotoxic, the doctors had no way to determine the cause to be gadolinium toxicity and the SFN was deemed to be idiopathic Small Fiber Neuropathy. No hope of treating the condition other than palliative for the pain. And no reporting of a contrast-related adverse event.

After telling members of the support group about the Small Fiber Neuropathy, we discovered 6 other people who have been diagnosed with Small Fiber Neuropathy. The prevalence of Small Fiber Neuropathy in the general population is 53 people per 100,000 according to a study done in Denmark <https://www.ncbi.nlm.nih.gov/pubmed/23997150>. Our group of 333 should have 0.18 people with SFN. We have 7 members who report a diagnosis of SFN, a prevalence of 2,100 per 100,000, and likely more if they were tested, since all of the respondents to our Symptom Survey identified pain as a symptom with 65% describing it as burning pain, numbness and tingling.

This, and similar seemingly over-prevalence for thyroid problems, tinnitus, vision problems and others described in our Symptom Survey should be investigated.



There is evidence of clinical implications of gadolinium deposition.

We have seen many new research papers regarding deposition of gadolinium from contrast MRIs since the Kanda Study published in December 2013. Some only deal with the mechanisms of deposition and detection of the gadolinium. Others deal with patient cases, both small cohorts and large retrospective studies of medical records. Those that deal with patient cases typically have some variation of the following sentence near the end of their document:

While we have evidence of the deposition of gadolinium in body tissue, there is no evidence of clinical implications of this deposition.

While they may have looked retrospectively, we could not find in any of these reports where they had actually talked to and examined the individuals. This is a huge gap in the search for clinical implications. Most of the symptoms we report do not result in a named condition that might be part of our medical records because they are not like symptoms from other causes and are often deemed non-specific. Some, like the electrified muscle vibrations, are even hard to describe to someone who has not experienced them. Attempts to use standard labels for these symptoms obfuscates some of the symptoms. A patient describing burning head pain that gets translated into "headache" is a misidentification of the symptom.

Just because the symptoms are hard to describe or are non-specific does not mean they aren't real, significant, and life-changing for the patient. But they will only be identified as clinical implications of gadolinium toxicity by talking with and examining those people who believe they have symptoms caused by retained gadolinium.

In addition to those who have made the connection from their symptoms to gadolinium from their contrast MRIs, we believe that there may be countless more people who have been affected by retained gadolinium but have not yet made the connection. That belief is based on numerous comments from people who have joined our support group after realizing that their unexplained symptoms were likely linked to their MRIs with a GBCA. In some cases, people's symptoms may be mild and just dismissed or blamed on whatever condition caused them to have their MRIs in the first place. That may be especially true of someone with MS or cancer, two conditions that result in frequent contrast MRIs. These conditions have been involved in some of the recent studies that reported finding evidence of gadolinium deposition in the brain but those conducting the study retrospectively may see no indication in patients' records of symptoms caused by gadolinium toxicity.

There is evidence of clinical implications. No one has looked for it in the place where it is most likely to be found, in the people who believe they are suffering from clinical implications.

FDA Action Required

In his introduction to the December, 2016 special issue of *Magnetic Resonance Imaging*, dedicated to Gadolinium Bioeffects and Toxicity, Dr. Emanuel Kanal, said the following about our website www.gadoliniumtoxicity.com :

There is a group of patients who over the past few years have gathered together in electronic format and who report sharing in common one attribute: That they believe that since they received a GBCA they have suffered significant health-related deterioration or symptoms that in their opinions are related to the gadolinium administration at least temporally, if not causally. While this is not the place to elaborate on their reported symptoms or this subject in general, it is worth noting that the number of individuals who share this commonality of complaint does seem to have grown over the past few years, and their common cause has more recently garnered the attention of organized radiology. While it is too early to assess the scientific veracity of some or all of their claims, extensive discussions with several individuals in this group by this author certainly does suggest that their concerns warrant being taken seriously and should invoke serious, formal, and prospective further study.

We believe we bring a lot of knowledge and experience to this issue. The information we provided makes the case that the FDA needs to take action. To summarize:

1. **Medical literature** documents toxicity of gadolinium and systemic implications.
2. **The Risk Factors** for adverse results are many.
3. **NSF-Like Symptoms** in patients with normal renal function.
4. **Gadolinium from GBCAs does not clear the body in a few days**, or even in a few months, allowing plenty of time for the gadolinium ion to dissociate from the chelate.
5. **Underreported Symptoms** from Contrast MRIs is a serious problem.
6. **There is evidence of clinical implications of gadolinium deposition.**

The actions we recommend include, but are not limited to:

1. Start by investigating suspected cases of Gadolinium Toxicity just like any other unexplained outbreak would be investigated - talk to and examine the patients who appear to have symptoms of Gadolinium Toxicity and evidence of gadolinium retention.
2. Fund urine testing studies to either confirm or refute the test results we have provided. This can be done quickly with a non-invasive study. When complete, provide information for clinicians and patients that will encourage the proper reporting of symptoms related to gadolinium toxicity.
3. Follow the European Medicines Agency path regarding the linear gadolinium-based contrast agents.

Thank you for your consideration of the information we have provided.

Sharon Williams
Hubbs Grimm