Gadolinium Toxicity - Let's not make the same mistake again

Editorial by Hubbs Grimm **August 2018**

I want to talk about the unfortunate results of the early studies of gadolinium toxicity that defined NSF and the parallels I see today in the effort to define Gadolinium Deposition Disease (GDD). I will also propose an alternative view of how to describe gadolinium toxicity in a way that reflects what we currently know and do not know that will recognize all patients who have been affected by retained gadolinium.

Before I begin, I want to be clear that I believe all those who have contributed in the past and those who are contributing today are doing so with the best of intentions and working from the basis of their experience and perspective. But that does not mean that the result or proposals are necessarily best for meeting the needs of the people who are suffering from the toxic effects of gadolinium.

The Errors of NSF

If we look back at NSF (Nephrogenic Systemic Fibrosis) - how it was named, how it was defined, the perceptions that have persisted based on its description - we can see how we got into the position we are in now, where clearly evident clinical symptoms of gadolinium toxicity are being denied and not even investigated. You can read more about how NSF came into being on our NSF Background page in the Background section.

From the definition of NSF as limited to people with severe kidney conditions who have specified dermatological features/fibrosis and meet a specific numeric result from the workup as defined by Girardi et al., several misconceptions have resulted and been adopted by the medical community. Let's look at what is wrong with present thinking.

- **NSF is not a disease of the kidneys.** - It is generally accepted that NSF is caused by gadolinium-released from gadolinium-based contrast agents (GBCAs) administered for a contrast-enhanced MRI and not caused by kidneys. Yet because of the name, Nephrogenic Systemic Fibrosis, doctors' and patients' first association is with bad kidneys. This served to inappropriately define the scope of damage caused by gadolinium to be limited to those people with bad kidneys.
- **Is it Black-and-White or a Disease-of-Degrees?** - One of our consistent themes in letters to the FDA, our research papers, and our presentation to the FDA committee meeting in September 2017 has been that NSF has illogically prescribed that the effects of retained toxic gadolinium

from contrast MRIs take on a black and white separation of "those who have it" and "those who do not" when a "disease of degrees" would be more appropriate and logical. For the renally impaired patients who, upon examination, fall just under the required score and are told they do not have NSF, are they to continue seeking the advice of more specialists to determine what they do have? This black and white approach further limited the scope of the negative impact of retained gadolinium to those who met the criteria.

- **NSF is not just about fibrosis** - While the dermal characteristics of NSF could be observed and tested, fibrosis is not the only impact of the gadolinium retained from contrast MRIs. The toxic effects of gadolinium have been well-documented in research papers to affect many other body systems. It is neuro-toxic, it affects the functioning of the mitochondria, it is a calcium channel blocker, it affects vascular reactivity, it has ocular effects. There are indications that it effects hearing, adrenal function, and others. What about those people affected more in these other systems but with less fibrotic activity? Is it at all right to say they have not been impacted by the free gadolinium?
- **Is NSF even a disease?** - Having a name for it only facilitates labeling and counting people that can be said to have NSF. NSF is not something that someone "gets". It is just a convenience for the medical community, an artificial line established along the continuum of gadolinium toxicity that serves to limit the number of cases and therefore the scope of the gadolinium problem. Having a name for it does not help all the patients who are affected, especially those who are affected but do not quite meet the diagnostic criteria for NSF.

Finally, regarding NSF, I tried to find the disease names associated with toxic levels of lead and mercury. I found no names (perhaps I did not look deeply enough). Just mercury poisoning and lead poisoning. When residents of Flint Michigan were affected by high levels of lead in their water system, no one decided to draw a line of some sort that says one person has lead disease and another person does not. Why? because it is accepted to be a disease of degrees. Lead poisoning has a list of symptoms that may occur so that they can be looked for, monitored, treated, and cared for, not to decide who has it and who doesn't.

[We have chosen to talk about gadolinium toxicity rather than gadolinium poisoning because it had been used in gadolinium-related literature. Toxicity also seems to be broader concept than poisoning. Poisoning evokes the feelings of "take a little and you die", for which we have not seen the evidence.]

Gadolinium Deposition Disease - Helpful or harmful idea?

Now we are looking at a new attempt to put a condition name on some limited set of people with normal renal function who have been affected by gadolinium and meet some specific conditions. The primary impact of this would be to limit the scope of what can be considered the clinical impacts of gadolinium toxicity. As described by Dr. Richard Semelka in recent web postings, those whose symptoms and onset timing meet the criteria he has chosen have Gadolinium Deposition Disease (GDD). What does this say for those whose symptoms have a different pattern but fall short of the criteria? Are they to understand that their symptoms are not from retained gadolinium? That should not be the case.

I want to challenge several of the concepts behind the criteria and definition of GDD. I have previously communicated directly with Dr. Semelka about my concerns.

- **Where is the proof that gadolinium only affects a small group of people?** - The presumptive thinking behind GDD is that gadolinium only affects a small group of patients, and GDD will define that small group. This presupposes the existence of two groups - those who are affected and those who are not (sounds like the thinking behind NSF). Where is the proof for this? If gadolinium toxicity is a disease of degrees like lead poisoning and mercury poisoning the impact to an individual can vary from a tiny bit to a severe situation. There are likely not two groups, and there is certainly no proof that these two distinct groups exist. To those who would say "but what about the millions and millions of people who have had contrast MRIs with no adverse affects", I would direct your thinking to those who said lead paint was safe because it had been used for millions of homes or those who said smoking was safe because of the millions who had smoked with no harm. Continuing to foster GDD merely enables doctors, manufacturers and regulatory agencies to maintain that gadolinium only effects a very small group of people and it is perfectly safe for everyone else.
- **Unjustified symptom and timing criteria** - Attempting to establish symptom and timing criteria without a large-scale study of patients is unjustified and harmful to suffering patients. While I appreciate the focus Dr. Semelka has brought to the symptoms of gadolinium toxicity, I take exception to some of his specific descriptions and the exclusion of some symptoms based on my communications with over 700 sufferers. The limitation that symptom onset must occur in the first 30 days is also unwarranted as it does not recognize the chronic harm done from many, many contrast MRIs wherein the symptoms were only recognized from the cumulative effect of the multiple exposures. With no large-scale study of sufferers, such specificity of who has GDD and who does not can only be characterized as arbitrary and harmful to those who do not meet the criteria. Such limitations produce one result: to limit the perceived scope of the harm caused by contrast MRIs.
- **The symptoms of gadolinium toxicity will vary from person to person, and no one should be excluded due to limited symptoms**. While we will likely never understand the causes completely, we know from the research literature and the symptoms of sufferers that gadolinium can cause neuropathic pain, other nervous system conditions, dermatological conditions, bone pain, ocular problems, etc. If a person has only one of these problems are they to be told they are just fine? We must not let GDD limit the perception of harm done by gadolinium from contrast MRIs.

In summary, I want to thank Dr. Semelka for bringing focus to the effects of retained gadolinium. However, I would urge him to focus on highlighting the broad symptoms, and not limit those who are affected but rather help doctors be open to the possibility of gadolinium as a cause of otherwise unexplained symptoms after patients' MRIs with contrast. The specificity of GDD is unwarranted based on gadolinium toxicity being a disease of degrees, just like all other forms of toxic poisoning.

An alternative view of Gadolinium Toxicity that is consistent with how the effects of other toxic substances are described.

Let me draw on the positioning of the overexposure to radiation from medical procedures and lead poisoning to recommend an alternative handling of gadolinium toxicity.

- **Radiation from x-Rays and CT Scans** - It is accepted that high doses of radiation from x-rays and CT scans can be harmful including increased risk of cancer, yet there is no named disease for those impacted. even though only some people are impacted. There are lists of side effects and advice to avoid exposure except when necessary as in these words from Harvard:

  > *Unless you were exposed to high doses of radiation during cancer treatment in youth, any increase in your risk for cancer due to medical radiation appears to be slight. But we don't really know for sure, since the effects of radiation damage typically take many years to appear, and the increase in high-dose imaging has occurred only since 1980.*
  >
  > *So until we know more, you will want to keep your exposure to medical radiation as low as possible. You can do that in several ways, including these:*
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  > - *Discuss any high-dose diagnostic imaging with your clinician.*
  > - *Keep track of your x-ray history.*
  > - *Consider a lower-dose radiation test.*
  > - *Consider less-frequent testing.*
  > - *Don't seek out scans.*
  >
  > *https://www.health.harvard.edu/cancer/radiation-risk-from-medical-imaging*

- **Lead Poisoning** - Although lead poisoning is now a recognized health risk that does not occur with the same symptoms or severity in all people with equal exposures, there is no disease named for those affected. A variety of symptoms may occur, and there are no criteria for those who have been affected. There are simply lists of symptoms that are not very specific in terms of identifying Lead Poisoning as can be seen from this list from the Mayo Clinic:

  > ***Lead poisoning symptoms in adults***
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  > *Although children are primarily at risk, lead poisoning is also dangerous for adults. Signs and symptoms in adults might include:*
  >
  > - *High blood pressure*
  > - *Joint and muscle pain*
  > - *Difficulties with memory or concentration*
  > - *Headache*
  > - *Abdominal pain*
  > - *Mood disorders*
  > - *Reduced sperm count and abnormal sperm*
  > - *Miscarriage, stillbirth or premature birth in pregnant women*

https://www.mayoclinic.org/diseases-conditions/lead-poisoning/symptoms-causes/syc-20354717

A description from Medscape describes Lead Poisoning this way:

> *Lead toxicity is a particularly insidious hazard with the potential of causing irreversible health effects. It interferes with a number of body functions primarily affecting the central nervous, hematopoietic, hepatic and renal system producing serious disorders. Acute toxicity is related to occupational exposure and is quite uncommon. Chronic toxicity on the other hand is much more common.*

https://emedicine.medscape.com/article/1174752-overview

With these descriptions as reference points, gadolinium toxicity has similar characteristics:

- Like lead, gadolinium is toxic to the human body and can even cause death in severe exposures
- While we know that a severe exposure can be morbid, we have no knowledge about a level of exposure that would be safe
- Gadolinium toxicity affects a wide spectrum of body systems and presents a variety of symptoms

Based on these two examples of how toxic substances are handled, Gadolinium Toxicity can be described in a way that reflects the reality of what we know and do not know that can be useful to all affected patients regardless of the breadth and severity of their symptoms. As a starting point for discussion of how such a description should read, I crafted the following description. I am not suggesting that this is complete or precisely accurate, but that a description of gadolinium toxicity could be in a form like this:

GADOLINIUM TOXICITY

Gadolinium toxicity can occur acutely or in a subtle or gradual way, but with harmful effects. Gadolinium does not naturally occur in the body and it can affect multiple body systems, being toxic to nerves, causing fibrosis of both skin and muscles, acting as a calcium channel blocker, depositing in the brain and in bones, as well as other locations. Acute toxicity includes Nephrogenic Systemic Fibrosis (NSF) but could occur outside the parameters used to define NSF. NSF has primarily affected patients with stage 4 kidney disease who received contrast MRIs. The systemic fibrosis of NSF has been morbid in severe cases and debilitating in other cases. Chronic gadolinium toxicity most often follows one or more contrast MRIs regardless of kidney function producing symptoms that reflect impacts to the body systems identified above.

The primary source of gadolinium toxicity is from contrast MRIs although it could occur in an industrial occupational setting. Anthropogenic gadolinium has been found in very small amounts in the water supply in some locales, but no cases of gadolinium toxicity have yet been published citing this source.

Gadolinium-Based Contrast Agents (GBCAs) administered for contrast-enhanced MRIs have been formulated by the manufacturer to attach the toxic gadolinium ions to other atoms to encase the

gadolinium ion. Gadolinium toxicity occurs when the complex breaks apart or dissociates, releasing the toxic gadolinium ion. The longer the GBCA remains in the body, the greater the opportunity for this to occur. In acute cases that were classified as NSF, the poor functioning of the patients' kidneys likely caused the GBCA to remain in the body well past the time period represented by the Agent's stability constant, causing the free gadolinium to be released. In chronic cases which can occur in patients with normal kidney function, smaller amounts of the toxic gadolinium ion are released in the body. Although chronic gadolinium toxicity can occur after one contrast-enhanced MRI, increased exposure from multiple doses of contrast increases the possibility of damage from free gadolinium that has been released from the GCBA.

Symptoms of gadolinium toxicity

Signs and symptoms of gadolinium toxicity may include the following:

- ***Neurological symptoms:*** *burning pain, tingling, feelings of something crawling under the skin*
- ***Dermatologic symptoms:*** *lesions, hyper pigmentation, skin thickening and tightening*
- ***Musculoskeletal Symptoms:*** *rapid muscle twitching, bone or joint pain, joint or muscle stiffness, muscle weakness, or a feeling of muscles being electrified*
- ***Cognitive symptoms:*** *brain fog, short-term memory issues*
- ***Ocular symptoms:*** *chronic dry eyes or rapidly worsening vision*
- ***ENT symptoms:*** *tinnitus or swallowing difficulty*
- ***Endocrine symptoms:*** *Low body temperature, extreme fatigue*

Presently there are no tests that can determine the amount of gadolinium in the body or the form of that gadolinium (free, as part of the GCBA, or in combination with other elements). While a 24-hour urine test for gadolinium can be done to determine how much is coming out every day, it does not determine how much remains in the body.

The chronic implications of gadolinium toxicity were first described in 2014 (Survey of the Chronic Effects of Retained Gadolinium from Contrast MRIs, Williams & Grimm) with little additional published research having been done to understand and document the symptoms, incidence, or prevalence. Lack of published research and the subtle nature of some chronic gadolinium toxicity symptoms may have led to underreporting of cases. As a result, we don't really know how to quantify the risk associated with a single contrast MRI, but with the risk increasing with multiple contrast MRIs, the potential risk should always be considered and compared with the diagnostic benefit of a contrast MRI, as an individual may have a greater need for a contrast MRI later in life.

So until we know more, you will want to keep your exposure to GBCAs as low as possible. You can do that in several ways, including these:

- Discuss any contrast-enhanced imaging with your clinician and the radiologist responsible for the procedure.
- Consider alternative imaging techniques.
- Keep track of your contrast MRI history including the agent and dosage received.
- Consider less-frequent testing in consultation with your doctors.
- Don't seek out contrast MRIs.

In Conclusion

In closing, I am not suggesting that the creation and acceptance of a description as outlined above would be the end of research efforts regarding the clinical effects of retained gadolinium. Quite the contrary, it would be the beginning of new research to prevent and treat such toxicity rather than research directed at limiting the scope of damage done by gadolinium-based contrast agents.

For a companion editorial on this topic by Sharon Williams, my partner on GadoliniumToxicity.com, read "*Gadolinium Toxicity - If not NSF then what is it?*".

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