



The Lighthouse Project

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shedding light on the effects of retained gadolinium from Contrast MRI

Gadolinium Toxicity: If not NSF, then what is it?

Editorial by Sharon Williams

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What difference does a name make? Evidently, when you are naming a disease it can make a huge difference. The name can limit the scope of medical research, and when it comes to gadolinium, it has the potential to exclude other patient populations who have been exposed to the same toxic metal.

In 1997, when a group of patients on dialysis developed what appeared to be a new skin disorder, it was called Nephrogenic Fibrosing Dermopathy (NFD). When researchers later learned that the problem went well beyond the patients' skin and caused a systemic disease process, the name was changed to Nephrogenic Systemic Fibrosis (NSF). The word "nephrogenic" in the name caused doctors and researchers to focus on people with severe renal disease. At the beginning, that made sense since the problem only had been seen in patients with end-stage renal disease (ESRD). Later we learned more about the cause.

In 2006, nine years after NSF/NFD was first diagnosed, the connection was made between NSF and gadolinium-based contrast agents (GBCAs) administered for MRIs. Even though impaired kidney function did not cause NSF, the focus remained on the "N" or nephrogenic part of NSF. Patients with normal kidney function were being overlooked; however, they were not unaffected by retained gadolinium from GBCAs.

In 2012, I wrote to the FDA about gadolinium retention in all patients, but especially those with normal kidney function who were being told that the unexplained symptoms they were experiencing after MRIs with a GBCA could not be caused by gadolinium because "people with normal kidneys don't retain gadolinium". I/we knew they were wrong about that, but because of what had been said repeatedly in the published literature, patients with normal kidney function could not convince doctors that their symptoms were connected to the MRI with contrast that they had. I believe that resulted in a gross underreporting of the health problems being caused by retained gadolinium.

Since early 2014, medical experts from around the world have slowly come to recognize that all patients who have MRIs with a GBCA likely retain an unknown amount of gadolinium in their brain, bones, skin, and other tissues. Even though retained gadolinium can cause NSF, researchers continue to say that they see no evidence that the gadolinium is having a harmful effect in patients with normal kidneys. As an affected patient with normal kidney function, I respectfully disagree.

In 2016, a paper was published that provided the initial description of what is being called Gadolinium Deposition Disease or GDD in patients with normal or near normal kidney function; the description was recently updated. The naming of GDD was a positive step for affected patients since it was the first time that gadolinium-related symptoms were recognized in patients with normal kidney function. However, I am concerned that the diagnostic criteria for GDD could result in some patients who have been affected by retained gadolinium not being recognized and properly diagnosed. Despite having evidence of prolonged gadolinium retention many months and even many years after their last MRI with a GBCA, those patients with only one or two chronic symptoms of gadolinium toxicity, or another disease such as MS, won't meet the diagnostic criteria for GDD. Like what happened with NSF, all patients affected by retained gadolinium may not be properly diagnosed, and the effects of gadolinium toxicity will continue to be underreported.

As of August 2018, governing authorities still have not recognized that patients with normal kidney function are being harmed by the gadolinium they are retaining. Researchers and the FDA want scientific evidence and not just anecdotal facts compiled from patients who have been affected by retained gadolinium. I understand the logic behind that, but don't we already have scientific evidence? After all, we have been down this road before with NSF/NFD. As more research was performed and more patient data was gathered, the evidence and understanding of what retained gadolinium can do to the human body has increased significantly. One only needs to read the NSF autopsy-based review articles to know that gadolinium can affect every organ in the body and cause extensive fibrosis and calcification of tissues. Isn't it logical to think that lesser amounts of retained gadolinium could cause similar but perhaps less severe damage to various body systems in almost every patient who retains it?

Instead of naming a "new" gadolinium-related disease, perhaps NSF should be renamed once again to make the name reflect the fact that impaired kidney function was not the cause of it. That is not a novel idea since it was suggested by some doctors in the past, including Dr. Jonathan Kay and his colleagues who said, "NSF neither originates in the kidney nor is caused by factors originating in the kidney". If we had known from the beginning in 1997 that retained gadolinium was the cause, maybe it would have been called gadolinium toxicity or gadolinium poisoning and not NFD or NSF.

I believe the "N" in NSF sent us down the wrong path and it has caused many patients who have retained gadolinium not to be properly diagnosed simply because they did not have impaired kidney function or NSF-like skin changes. We now know from the literature that *every* patient who has an MRI with contrast likely retains gadolinium. What we don't know is how much they retain.

Gadolinium Toxicity – A Disease of Degrees

I believe the problem is Gadolinium Toxicity, and not NSF, or anything else. As we have said many times before, Gadolinium Toxicity is a "disease of degrees" which we believe causes a disease process of varying severity with NSF likely being the most severe manifestation of it, but there is no reason to think it will be the only one. Depending on how much gadolinium someone retains and where it has been deposited in their body, the patient could experience many new symptoms or a few. The symptoms experienced could vary and might not be uniform among all patients.

A 2009 paper by Marckmann and Skov, "*Nephrogenic Systemic Fibrosis: Clinical Picture and Treatment*", provides some important insight into other aspects of NSF beyond just the expected biopsy findings. It describes "phases of NSF" and a "severity grading", and the paper highlights the differences between early and late manifestations of the disease. After reading the paper, it is evident that not all NSF patients presented clinically the same way. Why should patients with normal kidney function be expected to be any different when they retain gadolinium?

Several of the papers cited by Marckmann were referenced in my 2012 letter to the FDA to make my point that gadolinium retention could happen to ALL patients and they could be adversely affected by it. As Marckmann pointed out, "*supporting evidence of the causal relationship between GBCA and NSF comes from ex vivo and animal studies demonstrating that Gd-salts and some GBCAs cause histologic and clinical effects resembling what is seen in NSF*". They also said that "*it may be time to consider renaming NSF to what it really seems to be, which is Gd-induced systemic fibrosis*".

Gd-induced Systemic Fibrosis...If that name change had been made in 2009, perhaps gadolinium retention and the chronic symptoms and health issues experienced by patients with normal renal function would have been recognized much longer ago, and more time and resources could have been spent on trying to find a cure and better treatments for all affected patients. Instead, here we are 9 years later, and the scope of the gadolinium retention problem still has not been widely recognized.

Marckmann and Skov noted that the "*clinical picture of NSF is diversified*" and "*it varies from one patient to another and it varies over time*". They divided the clinical course of "GBCA-induced NSF" into 4 phases: latent (0-14 days after GBCA exposure with a range of 0-60 days), early inflammatory (14-60 days after GBCA with a range of 0-60 days), intermediate (60-180 days after GBCA exposure), and late fibrotic (+180 days after GBCA exposure). If that was the case in full-blown NSF, when the patient likely retained a lot more gadolinium, think how retaining less gadolinium might impact the clinical picture of patients with normal or near-normal renal function. Symptoms onset and severity could vary depending on how much gadolinium each person retained.

The authors made an important point that I believe should apply to all patients who have had MRIs with a GBCA. They said that the "*unusual clinical presentation and nonspecific histology means that it may be very hard to come to the NSF diagnosis in some patients. In practice, the diagnosis of NSF therefore sometimes has to be based primarily on patients' history of GBCA-exposures, subsequent appearance of otherwise unexplained symptoms from the skin, the limbs, or other organs, and the exclusion of relevant differential diagnoses*". That diagnostic criteria should be applied to every patient who has evidence of gadolinium retention after their MRI with contrast and *any* unexplained symptoms.

Gadolinium's toxic effects are well-documented

Do we need more research to understand the scope of the problem or just more awareness and acceptance of what has already been published about gadolinium toxicity and NSF?

We know from the NSF-related literature that gadolinium can cause a potentially fatal systemic disease process when it is retained in the human body. As Sherry et al. noted in their 2009 paper, "*A Primer on gadolinium chemistry*", one of the reasons why Gd^{3+} (gadolinium) is so toxic in biological systems, is because its ionic radius nearly equals that of Ca^{2+} (calcium), and because of that, gadolinium can

compete with calcium in all biological systems that require Ca^{2+} for proper function. The literature also indicates that gadolinium is neurotoxic, nephrotoxic, and cytotoxic, it inhibits mitochondrial function, induces oxidative stress, triggers endoplasmic reticulum stress, increases vascular reactivity, induces macrophage apoptosis, causes fatty liver, is a potent blocker of calcium channels, and more. With all of that published evidence of gadolinium's toxic effects, I don't believe it should come as a surprise to anyone that patients are reporting a wide range of symptoms after their MRIs with a gadolinium-based contrast agent – if anything, it seems it should be expected.

Here we are in 2018, 21 years after a problem first became apparent and 12 years after it was linked to gadolinium-based contrast agents. Let's not allow the name of a disease and how it is defined result in patients not having their gadolinium-induced symptoms and related health issues properly recognized and treated. Just as Marckmann and Skov said about NSF, the clinical picture of Gadolinium Toxicity is diversified, and it varies from one patient to another and it varies over time. The problem has nothing to do with patients' kidneys, but everything to do with retained gadolinium – a toxic metal like lead or mercury.

Evidence of gadolinium retention is evidence of harm.

I believe the time has come for researchers and the FDA to acknowledge that evidence of gadolinium retention is evidence of harm...period. It shouldn't matter whether the evidence comes from unenhanced brain MR images, gadolinium detected in biopsy specimens, prolonged gadolinium excretion in urine specimens, or other testing methods. Research efforts should focus on trying to find ways to mitigate the problem and treat the symptoms associated with Gadolinium Toxicity.

For more information about NSF, GBCAs, and Gadolinium, please see the Background section of our website. As you will see, Gadolinium Toxicity is not a new problem, but just one that should be recognized for the potential harm it can cause to everyone who retains gadolinium from the gadolinium-based contrast agents administered for MRIs.

For a companion editorial on this topic by Hubbs Grimm, my partner on GadoliniumToxicity.com, read "*Gadolinium Toxicity - Let's not make the same mistake again*".

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