

August 25, 2020

Open Letter to FDA, Radiologists & Researchers

Re: Symptoms of Gadolinium Toxicity

From: Sharon Williams, Coauthor of GadoliniumToxicity.com

Symptoms of Gadolinium Toxicity: Can their cause be explained?

When I wrote to the FDA in late 2012, I was concerned about the fact that gadolinium retention was not being recognized in patients with normal renal function (meaning eGFR >60). I provided numerous references from the published literature to support the points I made, including that there are ways gadolinium can get into the brain, that all patients are at risk of retaining gadolinium, that gadolinium is neurotoxic and could impair mitochondrial function and induce oxidative stress, that patients with normal renal function are excreting gadolinium long after their contrast-enhanced MRIs. These points and others made in my 2012 letter have been confirmed by subsequent published research.

However, the symptoms of gadolinium toxicity that patients are experiencing have not been recognized by the FDA or medical community as being caused by retained gadolinium (Gd). Part of the problem seems to stem from the fact that histopathological examination has not found any evidence that deposited Gd caused “harm” in the brain. However, one of the problems with the severe symptoms that some people complain of after exposure to Gd is that there is often no physical evidence, and the usual blood tests reveal no abnormalities. But what if Gd affected the function of cells, especially nerve cells, and triggered a cascade of adverse events, experienced by the person as decidedly abnormal and unpleasant sensations? Would that be easily detected on histological examination of tissue, or blood tests? The absence of physical and pathological evidence of abnormality, and the nature of the symptoms (which are often unusual and differ from one person to another) have been barriers to the acceptance that Gd is the cause of the symptoms. I believe there may be an explanation for these symptoms, which is what I am leading to in the discussion that follows.

Since it is relevant to the points I will be making, I would like to review some of what we already know about Gd from the literature, in terms of both its retention after administration and its effects at a cellular level.

Gd Retention

- Gd is a toxic metal that has no biological function in the human body. For use in MRIs as gadolinium-based contrast agents (GBCAs), the Gd³⁺ ion is bound to a linear or macrocyclic chelate to reduce its toxic effects.
- Retained Gd is recognized as the primary contributor to the development of nephrogenic systemic fibrosis (NSF) in patients with severely compromised renal function. Gd was found to affect all body systems. NSF is still not fully understood.
- Retention of Gd in patients with normal renal function was first recognized by the FDA on July 27, 2015.
- Evidence of Gd in the brain has been identified on MR images and in tissue specimens of patients with normal or near normal renal function. (Xia et al., 2010; McDonald et al., 2015; Kanda et al., 2015)
- Due to Gd remaining in patients' bodies, including the brain, for months to years after GBCA administration, the FDA required new class warnings for GBCAs on December 19, 2017.
- Neuronal tissue deposition of Gd after administration of a GBCA appears to be cumulative over a patient's lifetime & occurs in the absence of renal or hepatobiliary dysfunction. (McDonald et al., 2015)
- There is pathological confirmation of Gd retention in brain tissue of pediatric patients exposed to linear & macrocyclic GBCAs; Gd was generally highest in the globus pallidus (Stanescu et al., 2020).

- In rats, increased signal intensities in deep cerebellar nuclei persist for at least 1 year after administration of linear GBCAs with no elimination of Gd after week 5. Animals that received macrocyclic GBCAs showed ongoing elimination of Gd from the brain during the entire 1-year observation period. (Jost et al., 2018)
- In rats, after repeated injections of gadoterate (Dotarem), traces of intact chelated Gd were detected in the cerebellum one-year after last GBCA administration (Robert et al., 2018). One rat-year corresponds to approximately 30 years in humans (Sengupta, 2013).
- Studies with rats indicate that Gd that is no longer attached to the linear chelate cannot be cleared from the brain over time (Jost et al., 2017) & could remain in the brain permanently (Strzeminska et al., 2020).
- In healthy rats, retention of all 4 macrocyclic GBCAs in brain, bone, skin, liver, and kidney was demonstrated at 28 days (approx. 2.5 human years) after last exposure. Less Gd was retained in brain & soft body tissues 28 days after last exposure to ProHance. (Bussi et al., 2020)
- Intact ProHance was identified in NSF patient's skin biopsy 8 years after administration. (Birka et al., 2015)
- Gd deposition in normal brain & bone tissue occurs with macrocyclic & linear agents in patients with normal renal function. Bone levels measured 23 times higher (median) than brain levels. (Murata et al., 2016)
- Gd bone deposition was confirmed between 3 and 8 days after administration of a linear (Omniscan) & macrocyclic (ProHance) agent. (Gibby et al., 2004)
- Gd incorporated into bone, whether as free Gd^{3+} or as a chelate, may potentially be released back into the bloodstream by bone resorption and remodeling processes. Gd was detected in bone tissues longer than 8 years after GBCA exposure. (Darrah et al., 2009)
- Prolonged elimination of Gd was confirmed by urine testing. Based on elevated results at 30 days post-MRI, urine Gd levels are estimated to be >0.7 mcg/24 Hrs for more than 50 days after MRIs. (Alwasiyah et al., 2018)
- Prolonged deposition of Gd in tissues of patients with normal renal function was confirmed by increased Gd urine levels after intravenous administration of Ca/Zn-DTPA. The interval between the last MRI & DTPA therapy ranged from 2 to 94 months. (Semelka et al., 2018)

Gd entry into cerebrospinal fluid (CSF)

- A study in healthy rats demonstrated that all marketed GBCAs cross the blood-CSF barrier to an almost identical extent. The location of CSF infiltration is most likely the choroid plexus. (Jost et al., 2017)
- Gd is present in human CSF almost immediately after intravenous administration of gadobutrol (Gadavist) in both adult & pediatric patients even in the setting of normal renal function & no dysfunction of the blood-brain barrier (BBB). (Nehra et al., 2018)
- Gadoterate meglumine (Dotarem) easily penetrates into CSF regardless of renal function & in patients with intact BBB. Two patients in control group had GBCA-enhanced MRI more than 1 year before CSF extraction; Gd concentration 1 year later was 0.1 ng/mL & after 3 years it was 0.2 ng/mL. (Berger et al., 2018)
- Enhancement of the perivascular spaces in the basal ganglia was confirmed in subjects without renal insufficiency at 4 hours after a single dose of either ProHance or Omniscan. This might be a first step in the imaging evaluation of the glymphatic system (waste clearance system) of the brain. (Naganawa et al., 2017)
- Intrathecal administration of gadobutrol used as a tracer confirmed direct communication between CSF of the subarachnoid space & extravascular space of the human visual pathway. CSF tracer enrichment was found within the optic nerve, optic chiasm, optic tract, & primary visual cortex. The findings suggest the presence of a glymphatic system in the human visual pathway. (Jacobsen et al., 2019)

Effect on Inflammation & Macrophages

- Glycosaminoglycans (GAGs) or mucopolysaccharides play a central role in the signaling pathways of inflammatory processes. GAGs can transchelate with GBCAs and functional impairment of these signaling molecules could explain retention of Gd^{3+} in the body as well as the triggering of inflammatory processes as in NSF. (Taupitz et al., 2013)
- Low concentrations of GBCAs were shown to exert a variety of impacts on macrophages, indicating that GBCAs are capable of inducing several pathophysiological events that might be related to NSF or the accumulation of gadolinium in different tissues. (Weng et al., 2018)
- In mice with normal kidney function, GBCAs stimulate myeloid-induced renal fibrosis & subvert normal mitochondrial function in the kidney in a manner akin to common conditions such as obesity. (Do et al., 2019)
- Pro-inflammatory cytokine levels were elevated in patients with Gd retention. (Maecker et al., 2020)

Effect on Ion Channels

- The Gd^{3+} ion is toxic in biological systems due to having a nearly equal ionic radius to Ca^{2+} . The Gd^{3+} ion competes with Ca^{2+} and the trivalent ion binds with much higher affinity. (Sherry et al., 2009)
- Gd^{3+} can block voltage-gated Ca^{2+} , Na^+ & K^+ ion channels (Bourne & Trifaró, 1982; Elinder & Arhem, 1994; Lacampagne, et al., 1994; Zhang & Hancox, 2000; Adding et al., 2001).
- Gd^{3+} blocks stretch-sensitive ion channels (SAC) in sarcolemma of skeletal muscle fibers. Gd^{3+} affects $GABA_A$ and glutamate receptors. (Palasz & Czekaj, 2000)
- The amount of Gd^{3+} released from linear Gd-DTPA is sufficient to interfere with activity of human epithelial Na^+ channels' (ENaCs) activity, which could explain GBCA-related adverse events. (Knoepp et al., 2017)

Effect on neurons

- Gd affects intracellular calcium signaling in sensory neurons. (Baykara et al., 2019)
- GBCAs induce mitochondrial toxicity and cell death *in vitro* for basal-ganglia-type cells, and toxicity increases with decreasing kinetic stability of the contrast agent. (Bower et al., 2019)
- Gd can directly activate human nociceptive dorsal root ganglion (DRG) neurons. (Zhang et al., 2014)
- Gd was retained in the cerebrum, spinal cord, & peripheral nerves of rats exposed to multiple doses of gadodiamide (linear) & gadoterate meglumine (macrocylic). Gadodiamide led to heat & mechanical hyperalgesia in rats, suggesting the linear GBCA may have triggered the sensitization of spinal cord nociceptive neurons. (Alkhunizi et al., 2020)
- A recent study in mice found a possible link between small fiber neuropathy (SFN) & GBCA exposure. (Radbruch et al., 2020)

What does all that mean?

It means that Gd can quickly get into CSF and brain tissue of all patients, that it is being retained in the brain, bones, and other parts of the body for potentially years, and that it can adversely affect cells and biological systems. How might that retained gadolinium be causing symptoms?

The SFN & Gadolinium Toxicity connection

I am not a scientist or trained medical researcher, but a scientist told me that it can sometimes be helpful to look at things more simplistically. With that in mind, I set out to understand more about small fiber

neuropathy (SFN). On reading the recent study by Radbruch et al., which links GBCAs to SFN for the first time, I was struck by the similarity between the symptoms of SFN, described by Dr. Todd Levine (see below), and the symptoms described by people adversely affected by retained Gd.

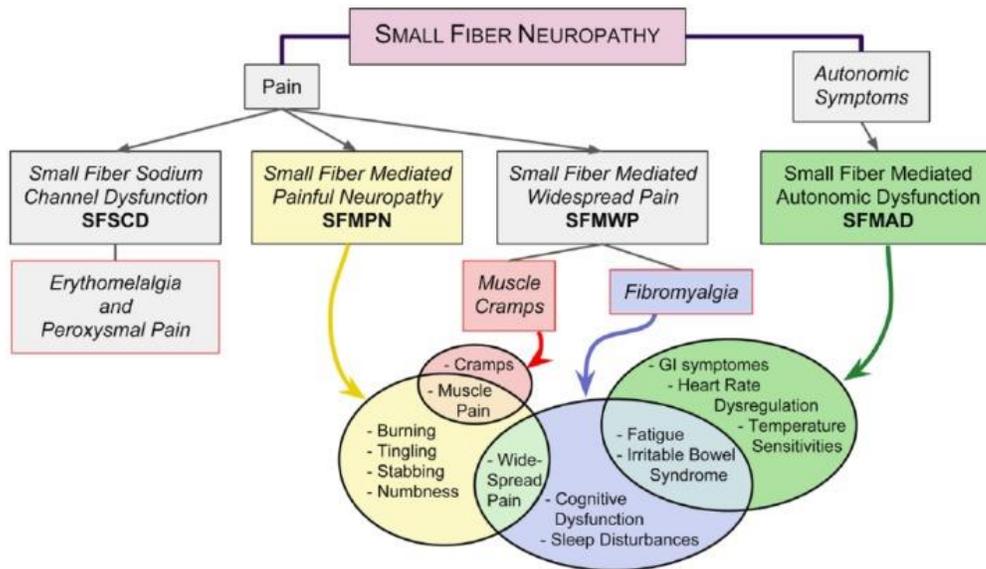
The following is an excerpt from *Small Fiber Neuropathy: Disease Classification Beyond Pain and Burning*, by Todd Levine, MD.

Small fiber neuropathy is the result of damage to peripheral nerves, including those that are small and myelinated (Aδ), as well as those that are unmyelinated (unmyelinated C fibers). In SFN, small somatic and autonomic fibers can be affected. Normally, these fibers control thermal and pain perception and control autonomic and enteric functions. For this reason, patients with SFN can present with either autonomic or somatic symptoms, or both. Symptoms are potentially numerous and can include allodynia, burning, lower thermal sensation, hyperesthesia, paresthesia, numbness in the lower extremities with potential to affect limbs and trunk, restless leg syndrome, dry eyes and mouth, abnormal sweating, bladder control issues, gastric issues, skin discoloration, and cardiac symptoms. Cardiac symptoms include syncope, palpitations, and orthostatic hypotension. Even without diffuse autonomic dysfunction, a percentage of patients with postural orthostatic tachycardia syndrome (POTS) can have SFN.

In another section, Levine describes other symptoms of SFN, including *muscle pain and cramps, headache, fatigue, irritable bowel syndrome, cognitive dysfunction, and sleep disturbances.*

There are a variety of diseases that may result in a small fiber neuropathy. Due to the variability of symptoms, Dr. Levine suggested that patients would benefit from determination of clinical phenotypes that allows for better diagnosis and treatment planning. He suggested using the following terms with the associated symptoms: small fiber sodium channel dysfunction (SFSCD), small fiber-mediated painful neuropathy (SFMPN), small fiber-mediated widespread pain (SFMWP), and small fiber-mediated autonomic dysfunction (SFMAD).

As can be seen in the diagram, there is some overlap of the symptoms among the different phenotypes suggested by Dr. Levine.



Reproduced from – “Small Fiber Neuropathy: Disease Classification Beyond Pain and Burning” by Todd D Levine. *Journal of Central Nervous System Disease*, Volume 10: 1-6, 2018.

As someone who has been affected by retained Gd for the last 10+ years, and has communicated with hundreds of other affected patients, I am extremely familiar with the symptoms of Gd toxicity that people

describe. Most of the symptoms in the SFN diagram have been described by these individuals. While burning pain is a common and distressing complaint, it is not the only one. People also complain of numbness, tingling, or prickling sensations (paresthesia); electric-like sensations; frequent itch; muscle twitches, spasms, and weakness; burning, dry eyes; abdominal pain and other GI issues; feeling extremely cold; skin changes including tightness, hyperpigmentation, papules, macules, and nodules; edema in extremities; a feeling of pain and pressure in the head that is unlike a headache; a new onset of “brain fog” and cognitive issues; difficulty regulating blood pressure; extreme fatigue; tinnitus; dysphagia.

Many of the clinical symptoms of NSF described in the literature and on the National Organization of Rare Diseases website are also like those associated with SFN (See Appendix 1 for Clinical Symptoms of NSF).

According to Terkelsen et al. (2017), SFN is a disease where the cause is unknown or idiopathic in up to 50% of the cases. It would be interesting to know how many of those patients had been injected with a GBCA prior to suffering symptoms that led to a diagnosis of SFN. I am not suggesting that all patients who have SFN have retained gadolinium; however, it is possible that in some patients with “idiopathic” SFN, retained Gd is responsible for their symptoms.

Nociceptors and Pain

The word “nociceptive”, which is mentioned in Radbruch’s paper about SFN and also in the paper by Maeker et al. (about increased serum cytokine levels in patients who had retained gadolinium), led me to the following information about the types of pain and the dorsal root ganglion. I believe it may explain some of what happens at a cellular level when Gd is retained and a cascade of adverse events is set into motion.

Nociception is the process by which intense thermal, mechanical, or chemical stimuli are detected by a subpopulation of peripheral nerve fibers, called nociceptors (Basbaum & Jessell, 2000).

Nociceptors are sensory neurons that detect signals from damaged tissue or the threat of damage and indirectly respond to chemicals released from the damaged tissue. Nociceptors are free (bare) nerve endings found in the skin, muscle, joints, bone, and viscera (Dafny, 2020). Nociceptors are excited only when stimulus intensities reach the noxious range. The cell bodies of nociceptors are located in the dorsal root ganglion (DRG) for the body and the trigeminal ganglion for the face (Basbaum et al., 2009). The DRG has an integral and important role in the modulation of peripheral and central sensory processing that includes inflammation, somatic pain, and the development of neuropathic pain (Krames, 2014).

Nociceptive pain is described as the most common type of pain and results from signaling of *noxious* or *potentially harmful stimuli* by nociceptors around the body and transmission of action potentials (APs) and warning signals to the spinal cord and brain (Krames, 2014). It represents the normal response to noxious insult or injury of tissues such as skin, muscles, visceral organs, joints, tendons, or bones (MedicalAcademic.co.za, 2020).

What if gadolinium is the noxious or harmful stimulus?

Neuropathic pain (NP) is described as the result of an injury or malfunction in the peripheral nervous system (PNS) or the central nervous system (CNS). NP, as chronic pain after peripheral afferent fiber (PAF) injury, is characterized by hypersensitivity resulting from decreased threshold to AP firing of nociceptors. With NP, this decreased firing threshold of nociceptors (hyperalgesia) occurs even from normal non-noxious stimuli (allodynia). This peripheral hyperexcitability is called peripheral sensitization. NP from peripheral sensitization is abnormal, aberrant, and chronic. (Krames, 2014) From the study by Alkhunizi et al. (2020), we know that Gd was retained in the spinal cord and peripheral nerves in rats exposed to multiple administrations of a linear (gadodiamide) and a macrocyclic (gadoterate meglumine) GBCA, with significantly more Gd being retained from the linear agent. Alkhunizi said that retention of Gd in the spinal cord and peripheral nerves might contribute to sensory symptoms and burning pain in the torso and extremities described by some patients after GBCA administration. What are the long-term effects of gadolinium retention in the CNS and PNS?

NP is described as frequent burning, piercing, stabbing, or electric shock sensations. The pain may persist for months or years beyond the apparent healing of any damaged tissues. In this setting, pain signals no longer represent an alarm about ongoing or impending injury; instead, the alarm system itself is malfunctioning. (MedicalAcademic.co.za, 2020)

After administration of a GBCA, I believe patients may be experiencing two types of pain: nociceptive and neuropathic. Most of the gadolinium toxicity affected patients I know describe their chronic pain as a dull, continuous ache, and as burning, numbness, prickling sensations, electric-like feelings, and/or deep bone pain in their hips, joints, and ribs. The often severe, distressing pain can disrupt a person's quality of life, and for some it is debilitating. I know patients who have been symptomatic for more than 10 years since their last MRI with a GBCA.

The Dorsal Root Ganglion (DRG)

Krames said the DRG contains the greatest proportion of the body's sensory neurons, cells that are primarily responsible for transduction of sensory information from the periphery and transmitting the information to the CNS. The cell bodies of DRG neurons do not interact with one another and are surrounded by layers of satellite glial cells (SGCs). The entire CNS and PNS are designed to protect and isolate its neurons from certain plasma molecules. The blood-brain barrier protects the CNS and the blood-nerve barrier protects and isolates the PNS. According to Hu et al. (2002), because the DRG is not protected by a blood-nerve barrier, small and large molecules and even macrophages can cross the SGC wrapping the DRG neurons.

A 2016 study by Godel et al. was the first *in vivo* investigation of physiologic and metabolic human DRG function indicated by quantitative parameters of DRG perfusion and permeability. The assessed perfusion parameter of blood-tissue permeability and leakage of contrast agent into the interstitial space were significantly increased in the DRG compared to the spinal nerve. Dotarem was the agent administered for the perfusion MRIs. Godel et al. noted that "an increased perfusion coupled with dense vascularization, the lack of tight junction proteins and the presence of large, endothelial fenestrations may synergistically contribute to an increased vulnerability of primary sensory neurons of the DRG to neurotoxic agents." This study confirms that GBCAs can get into the DRG.

From Zhang et al. (2014) and Baykara et al. (2019), we know that GBCAs and Gd have an adverse effect on DRG neurons. Zhang found that "gadolinium can directly activate a large population of human nociceptive DRG neurons." He noted that the "broad elevation of internal calcium level in DRG neurons can trigger various downstream events, such as abnormal sensations, and may contribute to the initiation of subsequent long-term physiological or pathological events, such as NSF." I think it is important to remember that NSF is more than just skin changes and joint contractures; according to Marckmann & Skov (2009), "skin changes and *neuropathic* symptoms predominate the early phase of NSF."

In Appendix 2, I am including a section of the 2014 Review Article, *The Role of the Dorsal Root Ganglion in the Development of Neuropathic Pain*, by Elliot S. Krames, MD, that will explain it in detail. The section is titled "Neuropathic Pain and the Role of the DRG." As you will see, it is also where the pro-inflammatory cytokines that were elevated in the study by Maecker et al. come into the picture. Appendix 2 also includes the first paragraph of the section of the paper that describes Na⁺, K⁺, and Ca⁺⁺ ion channels and the role they play in the development of neuropathic pain; from the literature, we know that Gd is a potent blocker of ion channels.

Might SFN and neuropathic pain explain the symptoms of Gd toxicity?

As Levine said, SFN can present with a wide variety of symptoms, due to somatic and autonomic fibers being affected. Normally, these fibers control thermal and pain perception and control autonomic and enteric functions. According to Purves et al. (2001), the visceral (or autonomic) motor system controls involuntary functions mediated by the activity of smooth muscle fibers, cardiac muscle fibers, and glands. It is regulated in part by circuitry in the cerebral cortex. In addition, the hippocampus, thalamus, basal ganglia, cerebellum, and

reticular formation all influence the visceral motor system. Gd deposition in various parts of the brain, especially the basal ganglia, has been confirmed by multiple studies, but has not, as yet, been connected to patients' symptoms.

Given that Gd has been shown to induce mitochondrial toxicity, interfere with ion channels, create neuronal hyperexcitability, and affect inflammatory processes, could Gd be affecting not only the part of the brain that controls many processes, but also peripheral and autonomic nerve endings, as well as dorsal root ganglia, to produce the many and varied symptoms that patients are experiencing?

With regard to the delay in the onset of symptoms in some people, could it be because the amount of Gd retained had not yet reached the threshold level required before nociceptors trigger a cascade of adverse events in the dorsal root ganglia at various levels, resulting in nociceptive and/or neuropathic pain? And does long-term deposition of Gd in bone, from which it may be constantly released back into the bloodstream by bone resorption and remodeling, provide an ongoing source of circulating Gd and perpetuation of symptoms that have been reported to last years after GBCA administration?

We know that retention of Gd has been demonstrated in humans, that unexplained symptoms are occurring, and the neuronal effects of Gd have been demonstrated experimentally. Could it just be that the connection has not yet been made, and when considered together, all these facts might explain how patients' symptoms are being caused by retained Gd from GBCAs?

In summary,

1. I have pointed out the similarity between the symptoms of SFN and those described by patients who believe they have been adversely affected by retained gadolinium, which are also like symptoms associated with NSF.
2. I have suggested that effects of Gd on nociceptors, at their nerve endings and at their cell bodies in the DRG, may be responsible for certain symptoms and long-standing neuropathic pain.
3. I have suggested an explanation for the variability of symptoms, their delayed onset in some people, and their long duration.

I realize the way our brain works is complex, but could there be a more simplistic explanation that links symptoms described by patients to the gadolinium they have retained?

The initial connection between SFN and GBCAs in mice was made by Dr. Radbruch and his colleagues. I hope that more research will be conducted that involves evaluation and testing of patients who have retained gadolinium and are experiencing SFN-like symptoms, which, until now, have been unexplained and perplexing to clinicians who are not familiar with the potential toxic effects of retained gadolinium.

Thank you for your time and consideration of this important matter, which many affected patients might describe as urgent. Please let me know if there is anything I can do to assist with your gadolinium-related patient research.

Sincerely,

Sharon Williams
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Enclosures:

Appendix 1 - Clinical Symptoms of NSF: More than skin changes & joint contractures, page 8
Appendix 2 - "Neuropathic Pain and the Role of the DRG", Elliott S. Krames, MD, page 9
Reference List - pages 10-13

Appendix 1 – Clinical Symptoms of NSF: More than skin changes & joint contractures

The following symptoms are described on the National Organization of Rare Diseases (NORD) NSF web page, and in a 2009 paper by Marckmann & Skov, *Nephrogenic Systemic Fibrosis: Clinical Picture and Treatment*.

NORD notes that NSF is characterized by thickening and hardening (fibrosis) of the skin, subcutaneous tissues, and, sometimes, underlying skeletal muscle. The proliferation of fibrotic tissue may become systemic, extending to other areas including the smooth, delicate membrane that surrounds the lungs (pleura), the sac surrounding the heart (pericardium), the thin sheet of muscle that aids respiration (diaphragm), and the outermost layer (dura mater) of the three membranes covering the brain and spinal cord.

According to Marckmann & Skov, approximately, 90% of NSF patients developed an erythematous rash; the skin turned reddish, bluish, or brownish in color. 80% of patients had marked, nonpitting swelling of the same areas. Skin changes are almost always localized to the limbs, primarily lower legs. 10% to 20% of patients had early involvement of hands or forearms. The face was usually spared, but according to Cowper et al. (2008), it was involved in 3% of the cases.

Most patients had their initial NSF-symptoms within 2 months after the “culprit” GBCA exposure. The mean delay was 14 days. However, 10% of patients experienced their first reaction to the GBCA within minutes or hours (immediate onset), whereas others had a latent phase of 4 weeks or even more.

NORD said the severity and progression of NSF can vary from one person to another. Additional symptoms associated with NSF were highly variable depending upon the specific organ system involved.

The following symptoms are also associated with NSF. Many are like those associated with small fiber neuropathy (SFN) and described by patients with normal renal function who have retained gadolinium.

- Pain – Almost 80% complained of pain, dysesthesia (burning, itching, electric-shock or buzzing sensations, & pins & needles) or hyperalgesia (an abnormally increased sensitivity to pain).
- Early neuropathic symptoms resolved to some extent. Some developed late signs of sensory & motor axonal neuropathy in the form of reduced sensibility & physical weakness of feet, legs, hands, & arms.
- Edema / swelling of the extremities
- Restless leg syndrome (seen in a minority of NSF patients)
- Muscle weakness often occurs in the early stage
- Muscle atrophy of the limbs is seen in the late stage
- Eyes may be red or blood shot in the early stage, with scleral plaques in the late stage
- Hair loss (diffuse)
- Gastrointestinal issues
- Rapid new onset fluctuating hypertension of unknown cause (Cowper, ICNSFR Website)
- Cardiac arrhythmia and portal hypertension
- Shortness of breath & lung-related issues
- Sleeplessness
- Anorexia (loss of appetite)
- Weight loss
- Depression

Note that “brain fog” and cognitive issues are symptoms many patients with normal renal function complain of, but both are missing from NSF-related symptoms. However, according to Seliger & Weiner (2013), cognitive impairment commonly occurs in patients with advanced kidney disease. Because of that, it may not have been considered a symptom of NSF.

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Appendix 2 – Excerpts from *The Role of the Dorsal Root Ganglion in the Development of Neuropathic Pain*, by Elliot S. Krames, MD, 2014. <https://doi.org/10.1111/pme.12413>

Abbreviations: APs (action potentials); ATP (adenosine-5'-triphosphate); DH (dorsal horn); DRG (dorsal root ganglion); NP (neuropathic pain); PAF (peripheral afferent injury); SGC (satellite glial cells); TNF (tissue necrosis factor)

Neuropathic Pain and the Role of the DRG (See Krames' paper for works cited in the following excerpts).

Nociceptive pain results from signaling of noxious stimuli by nociceptors and transmission of action potentials (APs) and warning signals to the spinal cord and brain. In contrast, NP, as chronic pain after PAF injury, is characterized by hypersensitivity resulting from decreased threshold to AP firing of nociceptors. With NP, this decreased firing threshold of nociceptors (hyperalgesia) occurs even from normal non-noxious stimuli (allodynia). This peripheral hyperexcitability is called peripheral sensitization. NP from peripheral sensitization is abnormal, aberrant, and chronic.

The development of NP is complex and involves the peripheral immune system, many different cell types that include DRG cell bodies, SGCs, glial cells, astrocytes and Schwann cells and neuronal pathways. A massive spontaneous discharge within large, axotomized A-neurons within the DRG occurs after cutting spinal nerves distal to the DRG. This and observations by Sukhotinsky et al. support the hypothesis that "ectopic firing in DRG A-neurons induces central sensitization" and clinical allodynia.

Scholz and Wolfe state that "NP has many of the features of a neuro-immune disorder". After injury to primary sensory neurons leading to NP, a host of pro-inflammatory mediators produced by Schwann cell and SGCs within the DRG are released and include eicosanoids, bradykinins, serotonin, neurotrophins, cytokines such as the interleukins, TNF- α , interferons, growth factors, and chemokines, ATP and reactive oxygen species.

Cytokines are glycoproteins that are mainly secreted by anti-inflammatory cells that include neutrophils, T-cells, and macrophages; however, they are also secreted by glial cells and Schwann cells within the DRG. These proteins are similar to prostanooids in that they have a relatively short half-life, are locally secreted in response to tissue damage (constitutive) and inflammation, and act to regulate the function of neighboring cells in response to tissue damage or inflammation. After tissue damage, glial cells and Schwann cells are activated and release a cascade of cytokines and other constitutive pro-inflammatory proteins that lead to inflammation and pain. The activation of these cells also leads to the production of pain mediators that sensitize and lower the threshold of glial cells to AP firing, leading to peripheral and central sensitization and chronic NP.

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Ion and Ion Channels and Pain: Na⁺, K⁺, and Ca⁺⁺ Channels and Neuropathic Pain (1st paragraph only)

DRG neurons express differing kinds of ion channels/receptors that have three main functions that include transduction, transmission, and modulation of sensory information. It is also important to note that, after PAF injury, DRG neurons become hyperexcitable, their SGC sheaths expand by numbers of cells and they exhibit ectopic firing. The ion channels and receptors at the peripheral terminals of DRG neurons involved in transduction of noxious information to electrical signals include transient receptor potential channels, Na⁺ channels, acid-sensing ion channels, and ATP-sensitive receptors. Channels produced that involve conduction through propagation of APs include Na⁺ and K⁺ channels. Modulation of synaptic transmission through regulation of the release of neurotransmitters is performed by voltage-gated Ca⁺⁺ channels and glutamate receptors, which are expressed on presynaptic membranes at the terminals of the primary afferents of the DH.

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