Signs & Symptoms after Gadolinium Administration: A Patient Survey
Report 1: Symptoms Paralleling Early-Phase NSF

Sharon Williams[1], Hubbs Grimm[1], Sarah Ratnam[2], Catriona Walsh (MB, BCh, BAO, MA)[3]
[1]Coauthor of GadoliniumToxicity.com, The Lighthouse Project
[2]Research Collaborator
[3]The Food Phoenix, Belfast, Northern Ireland
Correspondence: Sharon Williams; Sharon@GadoliniumToxicity.com

ABSTRACT

Background: The U.S. Food & Drug Administration (FDA) has acknowledged that after MRIs with a gadolinium-based contrast agent (GBCA), patients retain an unknown amount of gadolinium (Gd) in the brain, bone, skin, and other tissues, where it can remain for months to years. Although Gd is a toxic metal recognized as the primary cause of nephrogenic systemic fibrosis (NSF), harm attributed to long-term Gd retention in patients with normal renal function has not been recognized. This Patient Survey aims to address that issue.

Method: Members of Gd-related groups were invited to participate in this Patient Survey. 316 patients with normal or near-normal renal function who had experienced symptoms after an MRI with a GBCA completed a survey online, without any knowledge of the responses of the other participants. 185 of these patients had a laboratory test that confirmed Gd retention 30 days or longer after their last MRI (WITH) and 131 patients did not have Gd testing performed (WITHOUT). A third group was formed, comprised of 8 patients with biopsy-confirmed nephrogenic systemic fibrosis (NSF). In each patient group, reported symptoms were ranked in order of frequency. In the NSF Group, due to multiple symptoms having the same reporting frequency, the top 28 symptoms were used for comparison purposes.

Results: From a list of 60 symptoms, 19 of the 28 most frequently reported symptoms of the NSF Group were also ranked among the top symptoms reported by the two groups of Gd-exposed patients without renal impairment, indicating a substantial overlap in clinical presentation between what has been published about early-phase NSF and the post-GBCA symptom complex. Eleven of the 19 most frequently reported symptoms of the WITH, WITHOUT & NSF patient groups involve the nervous system. This pattern is also observed within a subgroup of 75 unconfounded cases (19 linear & 56 macrocyclic) comprised of patients who received a single GBCA and have confirmation of Gd retention (Tables 16 & 17). The symptoms reporting frequencies of the unconfounded subgroup strengthen the evidence presented within this Patient Survey that the symptom overlaps are genuine and not due to measurement error, exposure ambiguity, or bias. As with the clinical presentation of NSF (Table 10) and its variability in severity (Table 11), neuropathic symptoms predominate the early phase of the symptom complex reported by patients with normal renal function, and the severity of symptoms varies and can be life-altering in some patients.

Conclusion: These observations are consistent with the hypothesis that gadolinium exposure is associated with a spectrum of manifestations and underscore the need for standardized recognition, systematic clinical assessment, and further objective study of Gd-associated multisystem symptoms in all patient populations. Rather than a new or separate disease entity for patients with normal renal function, it seems that what we may be dealing with is one Gd-induced disease with varying degrees of severity, which is how NSF was described by Marckmann (2009). Symptom reporting frequencies indicate the nervous system may be most affected by Gd, possibly due to Gd having a particularly toxic effect on calcium channels, which was acknowledged by the FDA in a 2007 Memorandum (Appendix 4). The results of this Patient Survey warrant acknowledgement that retained gadolinium can cause harm in patients with normal renal function due to its recognized toxic effect on calcium channels.

Key Words: Gadolinium, gadolinium toxicity, GBCAs, NSF, normal renal function, symptoms, nervous system, calcium channels, unconfounded cases

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INTRODUCTION

Gadolinium-based contrast agents (GBCAs) have been used for contrast-enhanced magnetic resonance imaging (MRI) since the FDA approved the first GBCA, Magnevist® (Bayer HealthCare Pharmaceuticals), in 1988. However, gadolinium (Gd) is a toxic metal, which must be chelated or bound to a ligand before it can be administered as a contrast agent (Weinman et al., 1984; Mann, 1993). Once injected, the Gd ion can separate from the ligand and be deposited in patients' bones and other tissues. However, to the best of our knowledge, the long-term consequences of that deposition are still unknown due to a lack of research.

One of the mechanisms behind the toxic effects of the Gd^{3+} ion is that its ionic radius is very similar to that of calcium (Ca^{2+}), and it can compete with calcium in all biological systems and in some enzyme activity that requires Ca^{2+} for proper function, but with a much higher binding affinity (Sherry et al., 2009). Calcium plays an important role in regulating a great variety of neuronal processes (Berridge, 1998), and Gd is known to be a potent blocker of calcium channels (Bourne & Trifaró, 1982).

Differences between GBCAs are determined by the chemical structure of the chelator, with linear agents considered less stable and more likely to leave Gd in patients' bodies than macrocyclic agents (Morcos, 2008; Hao et al., 2012). However, both linear and macrocyclic GBCAs have been found to leave residual Gd in the body, including in the brain, bones, and skin of patients with normal renal function (Gibby et al., 2004; Xia et al., 2010; Murata et al., 2016). Higher levels of Gd have been found in bone than in the brain and skin (Murata et al., 2016; Kobayashi et al., 2021). Gadolinium deposited in bone could be released back into circulation during bone remodeling (Thakral et al., 2007; Darrah et al., 2009). Due to the lack of research, the effects of that release are unknown.

Initially, GBCAs were thought to be safe to use in all patient populations. However, by 1997, the first evidence of a problem appeared in patients with end-stage renal disease (ESRD) who were on dialysis and developed what was first described as a scleromyxoedema-like cutaneous disease (Cowper et al., 2000). In 2001, the new skin disorder was named Nephrogenic Fibrosing Dermopathy (NFD) (Cowper et al., 2001). By 2003, researchers had determined that the disease was not limited to dialysis patients, and it went well beyond the skin and caused a systemic disease process that affected multiple organs and tissues (Ting et al., 2003; Jimenez et al., 2004). It was then renamed Nephrogenic Systemic Fibrosis or NSF (Daram et al., 2005).

In 2006, nine years after evidence of a problem first appeared, the connection was made between NSF and the GBCA that had been administered for the patients' MRIs or MRAs (magnetic resonance angiography) (Grobner, 2006; Marckmann et al., 2006). Although NSF is still not fully understood, retention of Gd is recognized as the primary contributor to the development of NSF, which was found to affect all body systems to varying degrees (Mendoza et al., 2006). Even though impaired renal function was not necessarily the sole cause of NSF, for a long time, the focus of research remained on the "N" or nephrogenic part of NSF. Patients with normal renal function have felt their post-contrast MRI symptoms have not been taken seriously.

From 2006, when the NSF/GBCA connection was first made, until 2015, patients with 'normal' renal function, meaning an eGFR >60, were told they were not at risk of retaining Gd and their complaints of experiencing unusual symptoms after their MRIs were generally dismissed. However, after evidence of retained Gd was identified on brain images (Kanda et al., 2014) and in tissue specimens from patients with normal or near normal renal function (Kanda et al., 2015; McDonald et al., 2015), the FDA acknowledged on July 27, 2015, that patients with normal renal function were retaining Gd as well. Additional research was conducted and a public meeting on Gd retention was held on September 8, 2017, by the FDA Medical Imaging Drugs Advisory Committee (MIDAC). Faced with evidence that Gd was remaining in the body, including the brain, for months to years after contrast administration, the FDA required new class warnings for GBCAs on December 19, 2017. However, even though retained Gd is known to have caused NSF, the FDA has continued to state that it has not seen any evidence that the long-term retention of Gd causes 'harm' in patients with normal renal function. We address that issue in this report.

After reviewing NSF literature related to the clinical presentation of NSF, we realized symptoms reported by survey participants are like those described for early-phase NSF (Mendoza et al., 2006; Marckmann & Skov, 2009; Marckmann, 2011). In 2009, Marckmann wrote, "*skin changes and neuropathic symptoms predominate the early phase of NSF*", and "*there is a large variation in the type and intensity of symptoms between NSF patients, and symptoms also vary between early and late stages of the disease*."

The involvement of the nervous system and variability of symptoms, even among NSF patients, supports our belief that patients with normal renal function can be harmed by retained Gd in the same way as those with impaired renal function. We believe the symptoms results of this Patient Survey indicate we may be dealing with ONE disease with varying degrees of severity, not multiple Gd-induced diseases.

PATIENT SURVEY

Goals

As patient advocates, the study authors have had interactions with a significant number of patients who developed a consistent pattern of new symptoms soon after their MRIs with a GBCA. From those interactions, we know that many patients with normal renal function continue to be told that they are not at risk of retaining Gd, and urine test results, which proved otherwise, are still frequently being dismissed (Grimm & Williams, 2018; Alwasiyah et al., 2018; McDonald et al., 2025).

Patients describe experiencing many symptoms after exposure to a GBCA, but because their reporting is *subjective*, their concerns are often dismissed by healthcare providers rather than systematically evaluated for potential temporal association with GBCA administration. The scope of the problem has therefore not been fully recognized or investigated.

In conducting this survey, we had three goals:

- To provide sufficient new data to the FDA, other governing authorities, and researchers on Signs & Symptoms after GBCA administration so that a professional study would be conducted.
- To provide detailed symptoms and frequency data from more patients with suspected gadolinium-related adverse effects than has been previously reported in the peer-reviewed literature.
- To provide sufficient evidence of commonality between the symptoms reported by patients with normal renal function and those associated with Gd-induced NSF, so that the FDA recognizes that retained gadolinium may also cause harm in patients with normal renal function.

The results in this report provide important new data about symptoms reported by patients with normal and near normal renal function following MRIs with GBCAs, including temporal patterns and reporting frequencies across different agent types. For the first time, symptoms are reported by the type of agent administered for patients' last MRIs, and for patients who received only one GBCA (unconfounded cases) and have confirmation of Gd retention longer than 30 days.

While analyzing the survey results it became clear that there are many similarities between the clinical picture of NSF in its early phase and the symptoms reported by the participants in this Patient Survey. Because of these similarities, we decided to add a group of patients diagnosed with NFD/NSF; however, due to difficulty in finding NSF patients, the group is comprised of only 8 biopsy-confirmed cases including one from 2024. Seven of the NSF patients are from the U.S., and one is from Cyprus.

We believe the symptoms data presented in this report provide compelling evidence of commonality between the symptoms reported by survey participants and the clinical presentation of NSF as described by Marckmann & Skov (2009), particularly the neuropathic symptoms that predominate its early phase.

Methodology

Survey Questionnaire

The online Patient Survey was created using SurveyMonkey. The questions were developed based on what the authors have learned from their interactions with patients over the course of more than 14 years. The checkbox question about Symptoms included a list of 60 symptoms compiled from information patients have shared; from the symptom report by Williams & Grimm in 2014; from symptoms published by other authors on Gadolinium Deposition Disease (GDD) (Burke et al., 2016; Semelka et al., 2016) and from Symptoms Associated with Gadolinium Exposure (SAGE) (McDonald et al., 2021). Because GBCAs are administered intravenously and circulate systemically, gadolinium released from those agents can interact with multiple organ systems, making a broad and inclusive list of symptoms both appropriate and necessary. Input on the development of the questions was provided by two medical professionals.

The questionnaire included 8 Qualifying Questions & 9 Survey Sections:

Section 1 – Demographic Information
Section 2 – MRI History & Acute Symptoms
Section 3 – Symptoms Experienced after Last MRI
Section 4 – Signs of Systemic Abnormalities after Contrast MRIs
Section 5 – Other Abnormal Lab Results within 12 months of Patient's Last MRI
Section 6 – New Diagnoses / Autoimmune Diseases
Section 7 – Functional Disabilities & Other Limitations

Section 8 – Current Status of Symptoms & What treatments helped
Section 9 – Additional Comments (Responding was optional)

Survey results pertaining to Signs of Systemic Abnormalities (Section 4) will be presented in a separate report.

Symptom Reporting Frequencies

Symptom reporting frequencies were calculated as the percentage of participants reporting each of 60 symptoms within their respective patient groups (WITH, WITHOUT & NSF). The data was provided by SurveyMonkey in an Excel file containing the responses to each survey question. Rank order of symptom prominence was then determined and analyzed based on the reporting frequency within each group. Participants' individual responses were analyzed to determine symptom frequency by gender and by type of agent administered for the 75 patients in the Unconfounded Cases subgroup (Tables 16 & 17).

Patient Self-Reporting is valued by FDA & EMA

The online *Signs & Symptoms after Gadolinium Administration* survey questionnaire was comprised of checklists, multiple-choice, and open-ended questions. Both the FDA and European Medicines Agency (EMA) consider patient self-reports of adverse drug events (ADEs) an important additional source of information on the safety of drugs (FDA, 2020; EMA, 2022), and checklist-based questionnaires are more sensitive in identifying potential ADEs (de Vries et al., 2013).

Recruitment of Survey Participants

Members of online gadolinium-related groups, as well as patients referred by doctors providing chelation therapy, were invited to participate in this Patient Survey that was conducted in the summer/fall of 2024. Patients completed the survey without any knowledge of the responses of the other participants.

Two online surveys were conducted, one for patients with at least one test result that confirmed Gd retention and one for those who have not had testing performed. The two surveys were identical except for questions 6 and 8 about test results.

Participation criteria were established that required participants to answer 8 qualifying questions before they could access the survey questionnaire.

The same online survey was later used for the NSF group, but with changes made to three questions to ask how their diagnosis was made, renal status at the time of their diagnosis, and when they were diagnosed.

Participants were told that completion and electronic submission of the online survey questionnaire served as their voluntary agreement to allow their anonymous data to be used in this survey report and in future gadolinium-related research. Participants were assured that no identifying information would be shared with anyone without their prior written consent.

Survey Limitations

The limitations of this Patient Survey are the recruitment of participants from online gadolinium-related patient groups, the inability to independently confirm an individual's responses, and the small size of the NSF patient group (reflecting the inherent challenge of identifying affected patients in real-world settings and the privacy restrictions that prevent physician-based verification).

Survey Participants

A total of 324 participants took part in this Patient Survey: 316 patients with normal or near normal renal function and 8 with an NSF diagnosis.

WITH, WITHOUT & NSF are used throughout this report to identify the following patient groups:

WITH is for patients with a laboratory test confirming Gd retention.
WITHOUT is for those patients without a test confirming Gd retention.
NSF is for those who have been diagnosed.

All people in the NSF Group were diagnosed based on biopsy findings: 1 in 2003; 2 in 2006; 2 in 2008; 1 in 2015; 1 in 2020; 1 in 2024. The person diagnosed in 2020 had 1 MRI in 2005 while on dialysis.

Some participants answered through Section 3 about Symptoms but did not complete the remainder of the questionnaire. Survey participation for each patient group is reported in Table 1 below.

Table 1.	Survey Participation by Group		
Patient Group	Answered through Section 3	Answered through Section 4	Answered through Section 8
WITH Gd Test	185	177	172
WITHOUT Gd Test	131	113	109
NSF Diagnosis	8	7	7
Total	**324**	**297**	**288**

Reasons for Separate Survey Questionnaires

Conducting separate surveys for patients 'with' and 'without' a Gd test result serves two purposes:

- Similarities in symptoms rankings between the two groups could be used to support the belief of patients in the WITHOUT Group that their new, unexplained symptoms after MRIs are Gd-induced.
- Keeping survey results for patients WITH confirmation of Gd retention separate allows us to provide data and comparisons that are more likely to be recognized, particularly as it relates to Unconfounded Cases and NSF.

Where needed for comparison purposes, the results for the WITH and WITHOUT Groups are reported separately. Otherwise, the groups' responses are added together.

Qualifying Questions & Demographics

Participants were asked to provide a name or alias and an email address; none of that information will be disclosed. They were asked to confirm who was completing the questionnaire, confirm their renal status, enter their test results, and indicate if they are willing to share a copy of their test results, if needed for research purposes. Participants without a test result were asked to explain why they have never been tested for evidence of Gd.

Person Completing Questionnaire

305 patients from the WITH and WITHOUT Groups completed the survey themselves; in addition, it was completed by the parents of 7 children, 2 spouses, and a family member of 2 patients, one of whom was deceased. The total number of responses was therefore 316.

Renal Status at Time of MRI(s)

261 patients in the WITH & WITHOUT Groups confirmed they had normal renal function at the time of their MRIs.
6 patients did not have normal renal function (meaning they had an eGFR <60) at the time of their MRIs.
49 did not know their renal status at the time of the MRIs.

In the NSF Group (8 total):

2 patients were on dialysis	1 had a 'normal' eGFR	1 had an eGFR >50 but was acidotic and had DVT
1 had an acute kidney injury	1 had an eGFR >99	
1 needed a kidney transplant	1 did not remember	

Gender of Patients in the WITH & WITHOUT Groups

In general, we feel that women are more likely to join online support groups and respond to surveys, which may explain why more women than men participated in the patient survey. (The NSF Group was equally divided with 4 females & 4 males).

246 Females
68 Males
1 Preferred not to say
1 Self-described
316 Participants

Age at Time of Last MRI

Figure 1 shows the breakdown by age range for the 316 patients in the WITH & WITHOUT Groups at the time of their last contrast MRIs.

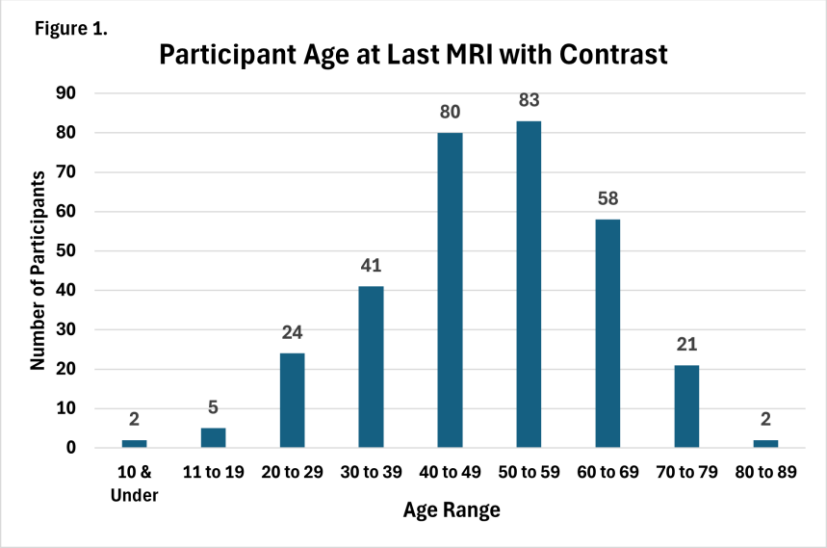


Table 2. Race or Ethnicity of Participants

	WITH	WITHOUT	NSF
East Asian	2	0	0
South Asian	4	1	0
Black or African American	3	1	0
Hispanic	5	5	0
Latino	2	2	0
Middle Eastern or North African	4	0	0
Multiracial or Multiethnic	0	2	0
Native American or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White	156	107	7
Prefer not to answer	3	6	0
Another race or ethnicity, please describe*	6	7	1
Total	**185**	**131**	**8**

* WITH Group, Another race or ethnicity: European American, Caucasian European descent, Ashkenazi Jewish white, Hebrew Ashkenazi, American, American Indian/American European.

WITHOUT Group, Another race or ethnicity: Mixed Caucasian & Hispanic, Chinese, Arabic, Native Métis & Fr. Canadian, American, Maltese, Italian. NSF Group, Another race or ethnicity: Greek Cypriot.

Geographic Location of Participants

Patients from around the world participated in the survey with 220 from the United States, including 7 from the NSF Group.

Below are the other countries and the number of respondents represented in the survey:
Algeria (1), Australia (12), Austria (3), Bulgaria (1), Canada (12), Chile (1), Cyprus (1), Finland (1), France (3), Germany (30), India (2), Israel (1), Latvia (1), Libya (1), Malta (1), Mexico (1), Netherlands (2), New Zealand (1), Norway (1), Poland (1), Slovenia (3), Switzerland (5), and UK (19).

Grouping of Participants

WITH Group – Gadolinium Test Results

Participants with test results were asked to enter the results from at least one test that confirmed they retained Gd 30 days or longer after their last MRI with a GBCA. The result could be from the testing of urine, blood, stool, skin, hair, nails, bone, or other tissue. Many patients entered results from multiple tests. The unit of measurement reported was not uniform from all countries and labs, but the results confirmed Gd retention. Due to medical privacy concerns, participants were not asked to provide copies of their test results.

Table 3a provides the breakdown for the types of testing the 185 participants in the WITH Group had performed. There were 282 test results entered. Although patients are excreting Gd in their urine for much longer than expected (Grimm & Williams, 2018; Alwasiyah et al., 2018), the results in Table 3b indicate that not all Gd is being eliminated in every patient.

Table 3a. Tests Confirming Gd Retention

Specimen Tested	# of Results Reported
Urine (unprovoked)	146
Urine (provoked)	62
Blood	19
Stool	12
Hair	10
Nails	2
Skin	4
Bone	4
Teeth	9
Sweat	2
Other tissues	12

Table 3b provides insight into the long-term retention of Gd in patients with normal renal function. Based on the results provided by survey participants, connective tissues and glandular tissues appear to show the greatest retention (this includes bone and teeth as well as cartilage and skin).

Table 3b. Gd Found in Connective & Glandular Tissues after Contrast MRIs

Patient ID #	Tissue Specimen Tested	Amount of Gd Detected	Time since Last Contrast MRI	LAST Agent Received & Number of MRIs
1*	Sigmoid colon	7.0 ng/g	13.6 years	Magnevist/ 5 MRIs/ unconfounded
	Bone – Lumber Spine	5,373 ng/g	11 years	
	Tissue & Muscle/lumbar spine	2,742 ng/g	11 years	
	Right Ovary	80 ng/g	9.8 years	
	Left Ovary	122 ng/g	9.8 years	
	Thyroid gland	211 ng/g	4 years	
2	Bone – Left Femoral Neck	21 ng/g	4 years	Dotarem/ 1 MRI
	Cartilage from Femoral Bone	34 ng/g	4 years	
	Skin	6 ng/g	17 months	
3	Jawbone	1,310 µg/kg	Not provided	Unknown Agents/ 2 MRIs
	Skin	106 µg/kg		
	Skin	37 µg/kg		
	Tooth	533 µg/kg		
	Tooth	978 µg/kg		
	Tooth	810 µg/kg		
	Tooth	1,470 µg/kg		
4	Tooth	2,180 mcg/kg	8 Years	Omniscan/ 5 MRIs/ confounded
	Tooth Root	940 mcg/kg	8 Years	

5	Uterus	8.0 µg/kg	1 year	Dotarem/ 16-20 MRIs/ confounded
	Tooth	1,710 µg/kg	1 year	
	Sweat	0.3 µg/l	2 years	
6	Bone - Pelvic	791 ng/g	14 years	Magnevist/ 1 MRI
7	Prostate	534 ng/g	22 years	Unknown Agents/ 4 MRIs
8	Skin	0.1 ng/g	5 years	Unknown Agents/ 5 MRIs
9	Nails	0.005 mg/kg	4.7 years	MultiHance/ 1 MRI
10	Nails	16 mg/kg	15.8 years	Magnevist/ 1 MRI
11	Tooth	40 µg/kg	Not provided	ProHance/ 2 MRIs/ confounded
12	Tooth (molar)	257 ng/g	Not provided	Gadovist/ 11 MRIs/ confounded
13	Sweat	0.6 µg/l	Not provided	Gadovist/ 6 MRIs/ confounded
14	Fat	5.0 ng/g	2.5 years	Dotarem/ 13 MRIs/ confounded
15	Abortion Material	0.06 mcg/g	3 years	Clariscan/ 1MRI
16	Eluate after 10th Dialysis	307 nmol/l	6 years	Unknown Agents/ 18 MRIs
17	Granuloma in Finger	4.0 ng/g	Not provided	Eovist/ 1 MRI

*** Disclosure:** Patient #1 is author SW.

Note: Test Results are Available to Researchers
167 of the 185 patients in the WITH Group indicated they are willing to share a copy of their test results with researchers. Patients are interested in participating in research that might shed light on how retained Gd is affecting the human body.

Tissue Repository

Developing a multiorgan tissue biorepository was suggested in McDonald et al.'s, 2018, "*Gadolinium Retention: A Research Roadmap*." However, to the best of our knowledge, it has not been created. That is unfortunate, since some of the specimens included in Table 3b were collected after 2018 from both linear and macrocyclic unconfounded cases.

WITHOUT Group – No Gadolinium Testing Performed

Participants without a test result were asked to explain why they have never been tested for evidence of Gd. More than one reason could be selected. Responses were as shown in Table 4.

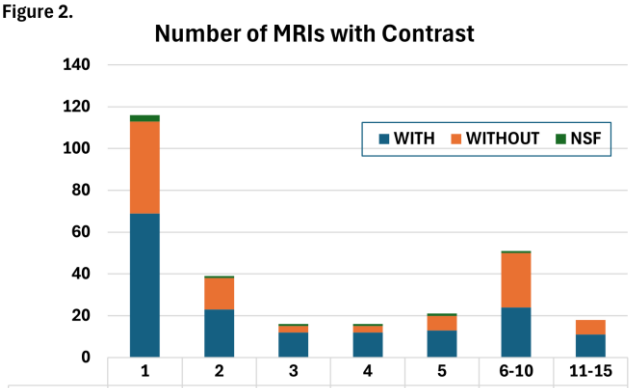
Table 4. Reason for Not Having Gd Testing Performed	**Responses**
My doctor refused to order a test.	26
I didn't know I could order a test online myself. *	52
I could not afford to order my own testing online. *	17
My test was performed long after my MRI & Gd was below detection limits.	5
Other – Had done testing but did not have the results	9
Other – Patients just learning about Gd retention problems	10
Other – Testing not available / easily accessible	7
Other – Thought exposure was too long ago for unprovoked testing	4
Other – Doctor didn't believe patient and/or know about Gd retention	5
Other – Patients waiting to do testing and get results	2
Other – Patient too ill and stressed to do another test	1

***** In the U.S., patients can order testing of urine, stool & hair at DirectLabs.com; the testing is performed by Doctor's Data.

Participant History with GBCAs

As shown below, more than one-third of respondents reported only a single MRI with a GBCA yet subsequently developed symptoms that led them to seek information and support from gadolinium-related patient groups. Many did so after receiving insufficient guidance in clinical settings, reflecting the limited awareness of potential adverse effects following GBCA administration. As can be seen in the NSF Group, even one dose of a GBCA can cause NSF.

Figure 2.



	1	2	3	4	5	6-10	11-15
NSF	3	1	1	1	1	1	0
WITHOUT	44	15	3	3	7	26	7
WITH	69	23	12	12	13	24	11

Informed Consent Document Prior to Contrast MRI

Based on patient feedback, we know that several patients feel that the Informed Consent documents that patients are asked to sign prior to their MRIs are inadequate when it comes to informing patients about potential risks associated with gadolinium retention and the document is not always provided to patients.

To gather data related to those issues, participants were asked if they signed an Informed Consent document that mentioned gadolinium. They were reminded that Medication Guides about gadolinium retention were not required by the FDA until 2018.

The responses of the 316 patients in the WITH & WITHOUT Groups are as follows:

- 56 Signed an Informed Consent document that did mention gadolinium.
- 59 Signed a document that did not mention gadolinium.
- 19 Signed an Informed Consent but their MRIs were before 2018 & Gd was not mentioned.
- 55 Were not given an Informed Consent document to sign prior to their MRIs.
- 82 Were not sure if they had been given an Informed Consent document to sign.
- 45 Provided other comments

In the NSF Group, only 2 signed an Informed Consent document.

Date of Last MRI

Patients were asked for the date of their last MRI. In the 1988 to 2000 Date Range, their MRIs were in 1998, 1999, and 2000. Those MRIs were 25+ years ago, yet the patients are symptomatic enough to still be active in an online Gd patient group.

Table 5.	**Total by Date Range for Last MRI**		
Date Range	**WITH**	**WITHOUT**	**NSF**
1988-2000	1	2	0
2001-2010	9	4	6
2011-2020	91	44	1
2021-2024	83	77	1
Yr not given	1	4	0
Total	**185**	**131**	**8**

In the NSF Group, 6 patients had their last MRIs between 2003 and 2006, 1 in 2015, and 1 in 2023.

The patients in 2015 and 2023 both had 'normal' renal function with one having an eGFR of 99. NSF is still being diagnosed and in patients with normal renal function.

Agent Administered for Last MRI

Table 6a presents information about the GBCA administered for participants' most recent MRI. The data show a predominance of macrocyclic agents, reflecting their broader adoption by radiology departments in recent years as part of a global shift away from linear GBCAs. While this trend is consistent with current clinical practice, the distribution in this survey may also be influenced by demographic factors, as individuals who underwent MRI examinations decades ago with linear agents are less likely to be represented due to age, health status, or reduced online engagement. Nevertheless, the symptom data presented in Tables 16 and 17 for patients who received only one GBCA may help clarify potential similarities or differences in adverse effects between linear and macrocyclic agents.

Table 6a. AGENT ADMINISTERED FOR LAST MRI

Answer Choices*	WITH	WITHOUT	NSF
Don't know the name of the agent I received	33	80	1
Ablavar®/Vasovist® (gadofosveset trisodium)	0	0	0
Clariscan™ (gadoterate meglumine)	8	9	0
Dotarem® (gadoterate meglumine)	44	14	0
Elucirem™ (gadopiclenol)	0	0	0
Eovist® (gadoxetate disodium)	2	0	0
Gadovist® (gadobutrol)	49	11	2
Gadobutrol® (generic, 2023)	1	0	0
Gadoterate Meglumine (generic, 2022)	0	0	0
Magnevist® (gadopentetate dimeglumine)	9	6	1
MultiHance® (gadobenate dimeglumine)	17	5	0
Omniscan® (gadodiamide)	5	1	4
OptiMark™ (gadoversetamide)	2	0	0
Primovist® (gadoxetic acid disodium)	1	0	0
ProHance® (gadoteridol)	13	4	0
Vueway® (gadopiclenol)	1	0	0
Other - Dotagraf	0	1	0
Total	**185**	**131**	**8**

* Appendix 1 contains GBCA trademark information

Table 6b. TYPE of GBCA ADMINISTERED for LAST MRI

Agent Type	WITH	WITHOUT	NSF
Name of Agent Unknown	33	80	1
Linear for Last MRI	36	12	5
Macrocyclic for Last MRI	116	39	2
Total	**185**	**131**	**8**

Symptoms after earlier MRIs

Participants who had multiple MRIs with contrast were asked if, in retrospect, they believed they experienced Gd-induced symptoms after their earlier MRIs. They were then asked if those symptoms caused them to have additional MRIs to investigate the new unexplained symptoms.

86 (47%) in the WITH Group & 54 (41%) in WITHOUT Group said that they experienced symptoms after their earlier MRIs.

42 (23%) in the WITH Group & 23 (18%) in WITHOUT Group said those symptoms caused them to have additional MRIs to investigate their new symptoms.

In the NSF Group, 4 of the 8 reported experiencing symptoms after earlier contrast MRIs that caused them to undergo additional MRIs, which resulted in their subsequent NSF diagnosis. These patients, suffering from initial symptoms of toxicity, were unfortunately exposed to more GBCAs, which are now recognized as the primary contributors to this life-altering iatrogenic disease.

Anaphylaxis & Severe/Acute Symptoms

Radiologists and MRI personnel are aware of and expected to document cases of anaphylaxis that manifest during or immediately after contrast administration. Nevertheless, there remains a critical information gap regarding patient outcomes and adverse events that occur after their discharge from the imaging facility. Here we provide data that, to the best of our knowledge, has never been reported based on information provided by the patient.

Anaphylaxis

19 patients in the WITH Group & 17 in the WITHOUT Group experienced a life-threatening allergic reaction (anaphylaxis) after contrast administration that required emergency medical intervention.

Severe/Acute Symptoms

Participants were asked if they experienced severe or acute symptoms immediately after or within a day or two after their MRIs that caused them to seek medical attention.

Table 7. Answer Choices	WITH		WITHOUT	
No	82	44%	75	57%
Yes, I saw my doctor	48	26%	25	19%
Yes, I went to ER or Urgent Care	55	30%	31	24%
Total	**185**		**131**	

In the NSF Group, 2 patients were hospitalized at the time of their MRIs, and 3 other patients sought medical care within a day or two of their MRI.

Additional ER Visits within 6 months of Last MRI

Participants were asked if they visited an ER at any other time within the first 6 months after their last MRI.

Table 8. Answer Choices	WITH		WITHOUT	
No	114	62%	92	70%
Yes (Briefly describe reason) *	71	38%	39	30%
Total	**185**		**131**	

* The reasons for ER visits include pain/ especially burning pain, deep bone pain, rib pain, muscle spasms, severe headaches/migraines, vertigo, liver pain, tachycardia, low blood pressure, high blood pressure, chest pain, palpitations, shortness of breath, nausea, and kidney pain.

In the NSF Group, 2 patients were hospitalized at the time of their last MRI, and 1 remained there for 3 months; two others visited the ER within the first 6 months. The reasons for their ER visits were chest pain, low blood pressure, heart issues, bone pain, rash, difficulty breathing, autonomic dysfunction, and adrenal issues.

Time between Last MRI & seeing a doctor.

129 or 70% of the WITH Group and 69 or 53% of the WITHOUT Group sought medical attention within the first month after their last contrast MRI.

Table 9. When Patient saw Doctor	WITH		WITHOUT		NSF	
The same day or the next day	31	17%	18	14%	3	37%
Within 1 week	56	30%	30	23%	2	25%
Within 1 month	42	23%	21	16%	0	0%
Within 3 months	21	11%	13	10%	2	25%
Within 6 months	8	4%	6	5%	0	0%
Within 1 year	4	2%	8	6%	1	13%
I did not seek medical attention within 1 year*	23	12%	35	27%	0	0%
Total	**185**		**131**		**8**	

***** Patients in the WITH & WITHOUT Groups said they did not know Gd, or the contrast agent could cause the symptoms they were experiencing. Some said the symptoms were like those they had after previous MRIs, and they thought they were just side effects. Some people were dealing with serious health problems, such as cancer, and did not associate their symptoms with the MRI until later.

Early-phase NSF Symptoms

To appreciate the significance of the survey results, one must know about the clinical presentation of NSF beyond skin changes and joint contractures, which are the 'visible' evidence of Gd-induced disease. We present relevant facts here.

According to observations made by Marckmann & Skov (2009), "*skin changes and neuropathic symptoms predominate the early phase of NSF*." As can be seen later in this report, symptoms involving the nervous system rank high in the NSF, WITH and WITHOUT groups. Other symptoms are also like those described in the NSF literature.

For reference, the early phase of NSF ranged from 14 to 60 days after GBCA exposure, with an intermediate phase of 60 to 180 days. The late phase of NSF was more than 180 days [6 months] after the patient's MRI (Marckmann & Skov, 2009).

Table 10. Early-phase Symptoms of NSF as described by Marckmann & Skov (2009) & Marckmann (2011):

- **Skin changes** - Rash, erythema, skin discoloration, itching, burning sensations, swelling that is often warm & painful. Localized to lower legs, forearms, hands, thighs, seldom trunk, and almost never face involvement. [*Note that Cowper et al., 2008, reported face involvement in 3% of NSF cases*].
- **Neuropathic symptoms** - 80% of patients complained of pain, dysesthesia [burning, itching, electric-shock sensations, and pins & needles] or hyperalgesia [increased sensitivity to pain]. Some presented with restless leg syndrome. Neuropathic symptoms may be so intense that the patient becomes physically disabled. Walking may become very painful.
- **Muscles** - Complaints of muscle weakness are common**.**
- **Bone** - Deep bone pain in the hips and ribs has been described.
- **Kidneys** - Reviews have concluded that nephrotoxicity may be seen with some GBCAs at a rate similar to that seen with iodine-based contrast agents.
- **Hair** - Diffuse hair loss in up to 50% of the patients
- **Intestines** - Acute gastroenteritis discomfort with pain, vomiting, and diarrhea soon after GBCA exposure.
- **Eyes** - 20% or more may present with red eyes as signs of noninfectious conjunctivitis
- **Lungs** - 15% developed acute pneumonia symptoms, including shortness of breath, hypoxia, and bilateral infiltrates on chest X-ray within a few days after GBCA exposure
- **Systemic Inflammation** - The initial phase of NSF frequently includes signs of systemic inflammation with fever, elevated C-reactive protein, elevated ferritin, anemia, and thrombocytosis or thrombocytopenia.

Other relevant points made by Marckmann and his colleagues are as follows:

- There is a large variation in the type and intensity of symptoms between NSF patients, and symptoms also vary between early and late stages of the disease.
- A minority of patients may have no or very mild symptoms, whereas others may present with very dramatic symptoms from one or more organs.

- In severe early-phase symptoms, patients may suffer from associated problems such as sleeplessness, depression, anorexia, and weight loss.
- Some GBCA-exposed patients develop some of the early-phase symptoms of NSF without progressing into the late and chronic phase of NSF [which they termed 'abortive or subclinical' NSF].
- Some NSF case reports indicate that symptoms may appear and progress even later.

Because the intensity and pattern of late-NSF symptoms varied 'enormously' among NSF cases, a severity scoring scale of 0 (no symptoms) to 4 (severely disabling symptoms) was proposed (Marckmann et al., 2008; Marckmann & Skov, 2009). The severity grading of NSF in Table 11 indicates that patients without joint contractures and severe disabilities, but with symptoms of gadolinium toxicity after their MRIs, may not have been properly diagnosed.

Table 11. Severity Grading (0-4) of NSF in its Late Phase (Marckmann & Skov, 2009)

Grade	Clinical Presentation	Comments [Marckmann's]
0	No symptoms	NSF cases with full symptom remission
1	Mild physical, cosmetic, or neuropathic symptoms not causing any kind of disability	These cases are easily overlooked
2	Moderate physical or neuropathic symptoms limiting physical performance to some extent	May remain mis- or undiagnosed
3	Severe symptoms limiting daily physical activities (walking, bathing, shopping, and so forth)	May remain mis- or undiagnosed
4	Severely disabling symptoms causing dependence on aid devices for common, daily activities	These cases are likely to be diagnosed and included in registry studies of NSF.

As a result of the unusual clinical presentation and nonspecific histology, Marckmann wrote that if 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 patient history of GBCA-exposures, subsequent appearance of otherwise unexplained symptoms from the skin, the limbs, or other organs, and the exclusion of relevant differential diagnose*s."

We believe those facts and others support our thinking about the significance of the symptoms data presented in this report.

Symptoms Results

To the best of our knowledge, we provide more Gd-related symptoms data than has been published previously. In addition to having data from more respondents, we report symptoms results for 19 linear and 56 macrocyclic unconfounded cases.

Unlike with NSF patients, skin changes are not the primary symptoms reported by the WITH and WITHOUT Groups. Because many ESRD patients received a double or triple dose of a linear GBCA prior to the onset of NSF (Grobner & Prischl, 2007), they may have retained more Gd than someone with normal renal function. However, that does not mean that the amount of Gd retained by patients with normal renal function is benign; the survey results indicate the opposite is true.

In the Symptoms Tables, a two-letter code identifies the body system associated with each symptom:

CS/Cardiovascular & Circulatory System	NS/Nervous System
DS/Digestive System	RS/Respiratory System
ES/Endocrine System	SS/Skeletal System
IS/Integumentary System	US/Urinary System

Results for the survey question about Symptoms after Contrast Administration are presented here in several tables.
To draw attention to symptoms involving the nervous system 'NS' is bold.

Table 12 – WITH Group presents symptoms data from 185 respondents WITH a Gd test result. Symptoms results are presented based on the type of GBCA administered for patients' LAST MRIs. (Unconfounded Cases are in Tables 16 & 17)

Table 12. SYMPTOMS / Within first 3 months after LAST MRI / WITH Result Group			Percentage calculated on Total MRIs by Agent Type							
			Total Responses		36 LINEAR		116 MACRO		33 UNKNOWN	
		Answer Choices (in order listed in survey)	#	%	#	%	#	%	#	%
1	*NS	Ache (dull continuous pain)	105	57%	22	61%	61	53%	22	67%
2	NS	Burning pain	128	69%	28	78%	77	66%	23	70%
3	NS	Numbness	89	48%	18	50%	54	47%	17	52%
4	NS	Tingling / Prickling sensations	146	79%	27	75%	93	80%	26	79%
5	NS	Low-level internal buzzing / electric-like sensations	98	53%	26	72%	53	46%	19	58%
6	NS	Head Pain (stabbing/ sharp/ localized head pain)	88	48%	19	53%	54	47%	15	45%
7	NS	Headache (atypical/new onset)	82	44%	19	53%	48	41%	15	45%
8	NS	Brain Fog / Cognitive Issues	134	72%	32	89%	75	65%	27	82%
9	NS	Migraine Auras	28	15%	8	22%	12	10%	8	24%
10	NS	Lightheadedness/ Dizziness	89	48%	21	58%	49	42%	19	58%
11	NS	Seizures	15	8%	4	11%	9	8%	2	6%
12	NS	Considered suicide/ suicidal ideation	45	24%	9	25%	28	24%	8	24%
13	NS	Muscle Spasms/ Cramps	106	57%	24	67%	56	48%	26	79%
14	NS	Muscle Twitching / Fasciculations	127	69%	28	78%	75	65%	24	73%
15	NS	Balance Issues	85	46%	20	56%	43	37%	22	67%
16	NS	Difficulty Walking	77	42%	18	50%	44	38%	15	45%
17	SS	Deep Bone Pain	105	57%	26	72%	62	53%	17	52%
18	SS	Pain in Joints	112	61%	27	75%	64	55%	21	64%
19	SS	Joint instability (clicking, popping, unstable joints)	60	32%	15	42%	33	28%	12	36%
20	SS	Pain in Ribs	67	36%	17	47%	38	33%	12	36%
21	IS	Skin Changes (hyperpigmented, mottled, or blotchy)	74	40%	21	58%	42	36%	11	33%
22	IS	Skin Rash	60	32%	18	50%	32	28%	10	30%
23	IS	Skin Lesions (such as ulcers, papules, macules, or nodules)	44	24%	14	39%	23	20%	7	21%
24	IS	Wrinkled skin (accelerated aging of skin)	73	39%	17	47%	44	38%	12	36%
25	IS	Itchy Skin	70	38%	15	42%	45	39%	10	30%
26	IS	Tight Skin	47	25%	12	33%	27	23%	8	24%
27	IS	Stretchy Skin	13	7%	4	11%	7	6%	2	6%
28	IS	Sagging Skin	31	17%	7	19%	19	16%	5	15%
29	CS	Hypotension (low blood pressure) (new onset)	27	15%	4	11%	19	16%	4	12%
30	CS	Hypertension (high blood pressure) (new onset)	34	18%	10	28%	16	14%	8	24%
31	CS	Labile Hypertension	11	6%	3	8%	5	4%	3	9%
32	CS	Tachycardia (fast heart rate)	71	38%	15	42%	45	39%	11	33%
33	CS	Arrhythmias (irregular heartbeat)	54	29%	13	36%	32	28%	9	27%
34	CS	Other Palpitations	47	25%	11	31%	28	24%	8	24%
35	CS	Chest Pain	56	30%	12	33%	33	28%	11	33%
36	RS	Shortness of Breath	65	35%	13	36%	43	37%	9	27%
37	CS	Edema (swelling of extremities)	33	18%	8	22%	16	14%	9	27%
38	DS	Digestive Symptoms (nausea, vomiting, diarrhea, etc)	90	49%	25	69%	51	44%	14	42%
39	DS	Abdominal Pain	61	33%	14	39%	36	31%	11	33%
40	US	Pain in Kidneys or Bladder	56	30%	13	36%	34	29%	9	27%
41	DS	Pain in Liver/Gallbladder Area	40	22%	10	28%	24	21%	6	18%
42	NS	Dysphagia (swallowing problems)	45	24%	15	42%	22	19%	8	24%
43	NS	Speech Difficulty/ Voice Changes	47	25%	16	44%	25	22%	6	18%
44	NS	Eye Redness	40	22%	9	25%	27	23%	4	12%
45	NS	Dry Eyes	72	39%	14	39%	49	42%	9	27%
46	NS	Floaters (eyes)	60	32%	15	42%	35	30%	10	30%
47	NS	Vision Changes / Blurry Vision	90	49%	23	64%	50	43%	17	52%
48	NS	Tinnitus (ringing in ears)	85	46%	18	50%	52	45%	15	45%
49	ES	Hair Loss	64	35%	16	44%	38	33%	10	30%
50	ES	Low Body Temperature	52	28%	9	25%	36	31%	7	21%
51	ES	Low-grade Fevers	16	9%	5	14%	9	8%	2	6%
52	ES	Fatigue	121	65%	24	67%	73	63%	24	73%
53	ES	Insomnia	96	52%	18	50%	60	52%	18	55%
54	ES	Loss of Appetite/ Anorexia	48	26%	9	25%	30	26%	9	27%
55	NS	Loss of Taste	14	8%	4	11%	8	7%	2	6%
56	RS	Flu-like Symptoms	42	23%	12	33%	21	18%	9	27%
57	NS	Metal Taste in Mouth	47	25%	10	28%	28	24%	9	27%
58	ES	Unexplained Weight Loss	47	25%	9	25%	31	27%	7	21%
59	ES	Unexplained Weight Gain	17	9%	6	17%	9	8%	2	6%
60	DS	Food intolerances (new)	40	22%	10	28%	23	20%	7	21%

* CS/Cardiovascular & Circulatory System; DS/Digestive System; ES/Endocrine System; IS/Integumentary System; **NS/Nervous System (bold)**; RS/Respiratory System; SS/Skeletal System; US/Urinary System

Total Respondents WITH Test Results **185** **36 Linear** **116 Macro** **33 Unknown**

Table 13. SYMPTOMS / Within 3 months of Last MRI			WITH Gd Results		Compare Results of WITH & WITHOUT Groups			WITHOUT Gd Results	
(WITH Group Responses sorted from high to low percentages)			#	%	(WITHOUT Group Responses sorted from high to low percentages)			#	%
1	*NS	**Tingling / Prickling sensations**	**146**	**79%**	**NS**	**Tingling / Prickling sensations**		**81**	**62%**
2	**NS**	**Brain Fog / Cognitive Issues**	**134**	**72%**	**NS**	**Brain Fog / Cognitive Issues**		**77**	**59%**
3	**NS**	**Burning pain**	**128**	**69%**	**NS**	**Burning pain**		**75**	**57%**
4	**NS**	**Muscle Twitching / Fasciculations**	**127**	**69%**	ES	Fatigue		69	53%
5	ES	Fatigue	121	65%	**NS**	**Muscle Twitching / Fasciculations**		**68**	**52%**
6	SS	Pain in Joints	112	61%	**NS**	**Numbness**		**66**	**50%**
7	**NS**	**Muscle Spasms/ Cramps**	**106**	**57%**	**NS**	**Muscle Spasms/ Cramps**		**66**	**50%**
8	**NS**	**Ache (dull continuous pain)**	**105**	**57%**	**NS**	**Ache (dull continuous pain)**		**62**	**47%**
9	SS	Deep Bone Pain	105	57%	**NS**	**Low-level internal buzzing / electric-like sensations**		**61**	**47%**
10	**NS**	**Low-level internal buzzing / electric-like sensations**	**98**	**53%**	**NS**	**Lightheadedness/ Dizziness**		**61**	**47%**
11	ES	Insomnia	96	52%	SS	Pain in Joints		**61**	**47%**
12	DS	Digestive Symptoms (nausea, vomiting, diarrhea, etc.)	90	49%	**NS**	**Balance Issues**		**59**	**45%**
13	**NS**	**Vision Changes / Blurry Vision**	**90**	**49%**	**NS**	**Head Pain (stabbing/ sharp/ localized head pain)**		**54**	**41%**
14	**NS**	**Numbness**	**89**	**48%**	IS	Itchy Skin		**54**	**41%**
15	**NS**	**Lightheadedness/ Dizziness**	**89**	**48%**	**NS**	**Tinnitus (ringing in ears)**		**53**	**40%**
16	**NS**	**Head Pain (stabbing/ sharp/ localized head pain)**	**88**	**48%**	ES	Insomnia		**52**	**40%**
17	**NS**	**Balance Issues**	**85**	**46%**	SS	Deep Bone Pain		**50**	**38%**
18	**NS**	**Tinnitus (ringing in ears)**	**85**	**46%**	DS	Digestive Symptoms (nausea, vomiting, diarrhea, etc.)		**49**	**37%**
19	**NS**	**Headache (atypical/new onset)**	**82**	**44%**	IS	Hair Loss		**49**	**37%**
20	**NS**	**Difficulty Walking**	**77**	**42%**	**NS**	**Headache (atypical/new onset)**		**47**	**36%**
21	IS	Skin Changes (hyperpigmented, mottled, or blotchy)	74	40%	RS	Shortness of Breath		45	34%
22	IS	Wrinkled skin (accelerated aging of skin)	73	39%	IS	Skin Changes (hyperpigmented, mottled, or blotchy)		44	34%
23	**NS**	**Dry Eyes**	**72**	**39%**	**NS**	**Vision Changes / Blurry Vision**		**43**	**33%**
24	CS	Tachycardia (fast heart rate)	71	38%	**NS**	**Dry Eyes**		**40**	**31%**
25	IS	Itchy Skin	70	38%	IS	Skin Rash		39	30%
26	SS	Pain in Ribs	67	36%	SS	Pain in Ribs		36	27%
27	RS	Shortness of Breath	65	35%	CS	Chest Pain		36	27%
28	IS	Hair Loss	64	35%	**NS**	Difficulty Walking		34	26%
29	DS	Abdominal Pain	61	33%	**NS**	Floaters (eyes)		34	26%
30	SS	Joint instability (clicking, popping, unstable joints)	60	32%	**NS**	Metal Taste in Mouth		34	26%
31	IS	Skin Rash	60	32%	IS	Wrinkled skin (accelerated aging of skin)		32	24%
32	**NS**	Floaters (eyes)	60	32%	SS	Joint instability (clicking, popping, unstable joints)		30	23%
33	CS	Chest Pain	56	30%	**NS**	Dysphagia (swallowing problems)		30	23%
34	US	Pain in Kidneys or Bladder	56	30%	DS	Abdominal Pain		29	22%
35	CS	Arrhythmias (irregular heartbeat)	54	29%	CS	Tachycardia (fast heart rate)		27	21%
36	ES	Low Body Temperature	52	28%	CS	Edema (swelling of extremities)		27	21%
37	ES	Loss of Appetite/ Anorexia	48	26%	DS	Food intolerances (new)		27	21%
38	IS	Tight Skin	47	25%	**NS**	Migraine Auras		26	20%
39	CS	Other Palpitations	47	25%	RS	Flu-like Symptoms		26	20%
40	**NS**	Speech Difficulty/ Voice Changes	47	25%	CS	Other Palpitations		25	19%
41	**NS**	Metal Taste in Mouth	47	25%	CS	Arrhythmias (irregular heartbeat)		24	18%
42	ES	Unexplained Weight Loss	47	25%	US	Pain in Kidneys or Bladder		24	18%
43	**NS**	Considered suicide/ suicidal ideation	45	24%	ES	Low Body Temperature		24	18%
44	**NS**	Dysphagia (swallowing problems)	45	24%	ES	Unexplained Weight Loss		24	18%
45	IS	Skin Lesions (such as ulcers, papules, macules, or nodules	44	24%	IS	Tight Skin		23	18%
46	RS	Flu-like Symptoms	42	23%	ES	Loss of Appetite/ Anorexia		21	16%
47	DS	Pain in Liver/Gallbladder Area	40	22%	**NS**	Speech Difficulty/ Voice Changes		19	15%
48	**NS**	Eye Redness	40	22%	**NS**	Eye Redness		19	15%
49	DS	Food intolerances (new)	40	22%	ES	Unexplained Weight Gain		18	14%
50	CS	Hypertension (high blood pressure) (new onset)	34	18%	**NS**	Considered suicide/ suicidal ideation		17	13%
51	CS	Edema (swelling of extremities)	33	18%	CS	Hypertension (high blood pressure) (new onset)		17	13%
52	IS	Sagging Skin	31	17%	IS	Sagging Skin		16	12%
53	**NS**	Migraine Auras	28	15%	DS	Pain in Liver/Gallbladder Area		16	12%
54	CS	Hypotension (low blood pressure) (new onset)	27	15%	IS	Skin Lesions (such as ulcers, papules, macules, or nodules		15	11%
55	ES	Unexplained Weight Gain	17	9%	ES	Low-grade Fevers		12	9%
56	ES	Low-grade Fevers	16	9%	CS	Hypotension (low blood pressure) (new onset)		10	8%
57	**NS**	Seizures	15	8%	**NS**	Loss of Taste		9	7%
58	**NS**	Loss of Taste	14	8%	IS	Stretchy Skin		8	6%
59	IS	Stretchy Skin	13	7%	**NS**	Seizures		6	5%
60	CS	Labile Hypertension	11	6%	CS	Labile Hypertension		6	5%

* CS/Cardiovascular & Circulatory System; DS/Digestive System; ES/Endocrine System; IS/Integumentary System; **NS/Nervous System (bold)**; RS/Respiratory System; SS/Skeletal System; US/Urinary System

Total Respondents WITH Test Results 185 **Total Respondents WITHOUT Test Results 131**

Table 13 – **WITH and WITHOUT Groups** shows symptom responses sorted from high to low based on percentages. Symptoms linked to NS, or the Nervous System, make up 64% of the top 25 symptoms listed for the WITH Group and 60% of the top 25 for the WITHOUT Group. **Our Assessment:** The similarity in the pattern and prevalence of their top-reported symptoms supports the hypothesis that the two groups represent a similar patient population experiencing the same underlying condition after their MRIs with a GBCA.

Figure 3 provides a different perspective of the symptoms data presented in Table 14. Due to multiple symptoms in the NSF Group having the same reporting frequency, we compared the top 28 symptoms of the NSF, WITH and WITHOUT Groups. The 3 groups had 19 of the same symptoms in their top 28, 11 of which involve the nervous system

Figure 3.

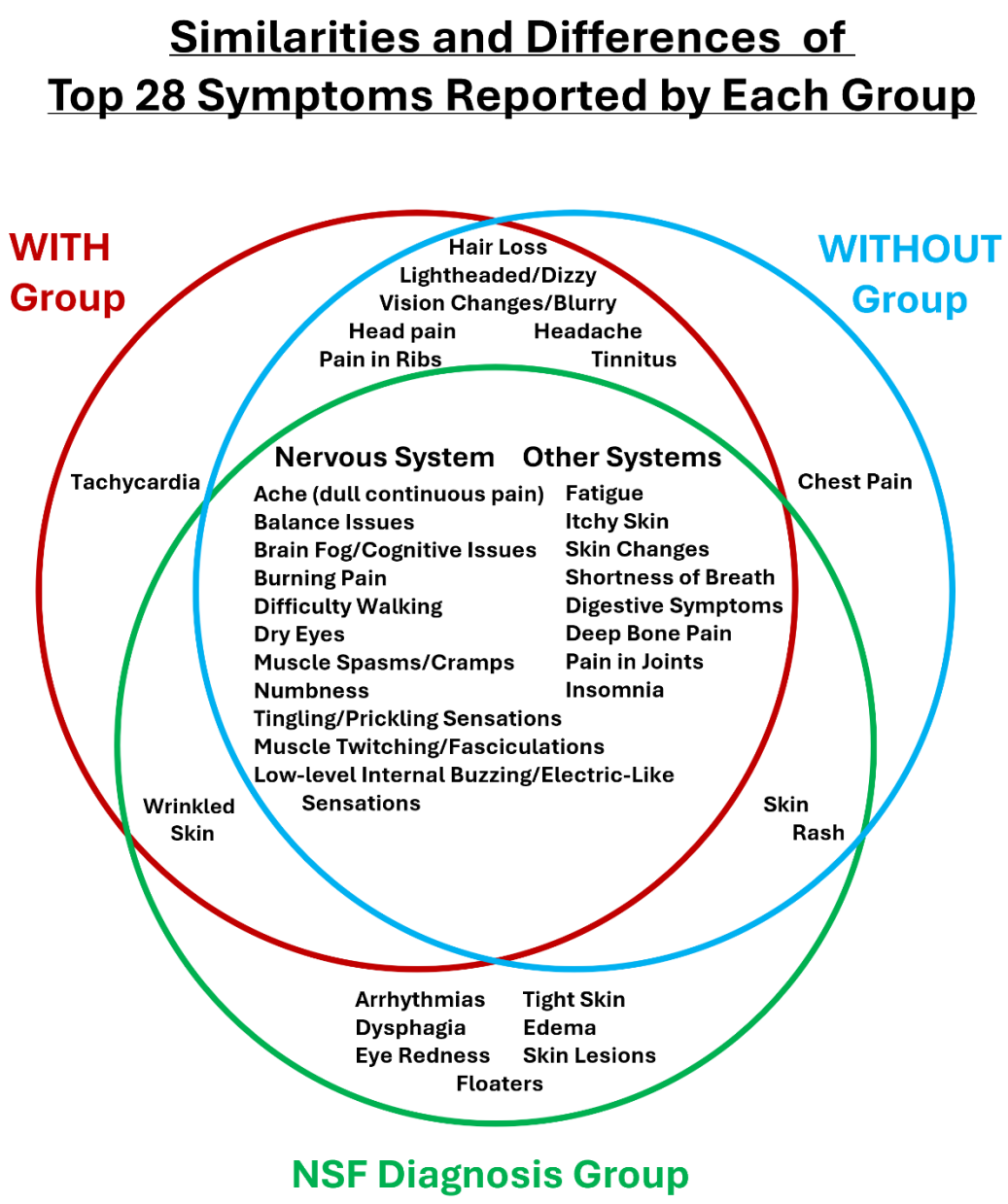


Table 14. COMPARISON of SYMPTOM RANKINGS TO NSF GROUP		NSF GROUP		WITH GROUP		WITHOUT GROUP	
Highlighted Symptoms in WITH & WITHOUT Groups are in NSF Group's Top 28		Ranking	%	Ranking	%	Ranking	%
IS*	Skin Changes (hyperpigmented, mottled, or blotchy)	1	100%	21	40%	22	34%
NS	**Difficulty Walking**	2	88%	20	42%	28	26%
IS	Tight Skin	3	88%	38	25%	45	18%
ES	Fatigue	4	75%	5	65%	4	53%
NS	**Brain Fog / Cognitive Issues**	5	63%	2	72%	2	59%
NS	**Muscle Spasms/ Cramps**	6	63%	7	57%	7	50%
SS	Deep Bone Pain	7	63%	9	57%	9	47%
IS	Skin Rash	8	63%	31	32%	25	30%
IS	Skin Lesions (such as ulcers, papules, macules, or nodules)	9	63%	45	24%	54	12%
IS	Wrinkled skin (accelerated aging of skin)	10	63%	22	40%	31	24%
IS	Itchy Skin	11	63%	25	38%	14	41%
CS	Edema (swelling of extremities)	12	63%	51	18%	36	21%
NS	**Ache (dull continuous pain)**	13	50%	8	57%	8	47%
NS	**Burning pain**	14	50%	3	69%	3	57%
NS	**Tingling / Prickling sensations**	15	50%	1	79%	1	62%
SS	Pain in Joints	16	50%	6	61%	11	47%
NS	**Eye Redness**	17	50%	48	22%	48	15%
NS	**Dry Eyes**	18	50%	23	39%	24	31%
NS	**Numbness**	19	38%	14	48%	6	50%
NS	**Low-level internal buzzing / electric-like sensations**	20	38%	10	53%	9	47%
NS	**Muscle Twitching / Fasciculations**	21	38%	4	69%	5	52%
NS	**Balance Issues**	22	38%	17	46%	12	45%
DS	Digestive Symptoms (nausea, vomiting, diarrhea, constipation, bloating, re	23	38%	12	49%	18	37%
ES	Insomnia	24	38%	11	52%	16	40%
RS	Shortness of Breath	25	38%	27	35%	21	34%
NS	**Dysphagia (swallowing problems)**	26	38%	44	24%	33	23%
NS	**Floaters (eyes)**	27	38%	32	32%	29	26%
CS	Arrhythmias (irregular heartbeat)	28	38%	35	29%	41	18%
NS	**Lightheadedness/ Dizziness**	29	25%	15	48%	10	47%
SS	Joint instability (clicking, popping, unstable joints)	30	25%	30	32%	32	23%
IS	Stretchy Skin	31	25%	59	7%	58	6%
IS	Sagging Skin	32	25%	52	17%	52	12%
CS	Tachycardia (fast heart rate)	33	25%	24	38%	35	21%
CS	Other Palpitations	34	25%	39	25%	40	19%
CS	Chest Pain	35	25%	33	30%	27	28%
DS	Abdominal Pain	36	25%	29	33%	34	22%
NS	**Vision Changes / Blurry Vision**	37	25%	13	49%	23	33%
NS	**Tinnitus (ringing in ears)**	38	25%	18	46%	15	41%
ES	Hair Loss	39	25%	28	35%	19	37%
NS	**Loss of Taste**	40	25%	58	8%	57	7%
RS	Flu-like Symptoms	41	25%	46	23%	39	20%
ES	Unexplained Weight Loss	42	25%	42	25%	44	18%
NS	**Head Pain (stabbing/ sharp/ localized head pain)**	43	13%	16	48%	13	41%
NS	**Migraine Auras**	44	13%	53	15%	38	20%
NS	**Seizures**	45	13%	57	8%	59	5%
SS	Pain in Ribs	46	13%	26	36%	26	28%
CS	Hypotension (low blood pressure) (new onset)	47	13%	54	15%	56	8%
CS	Labile Hypertension	48	13%	60	6%	60	5%
US	Pain in Kidneys or Bladder	49	13%	34	30%	42	18%
NS	**Speech Difficulty/ Voice Changes**	50	13%	40	25%	47	15%
ES	Low Body Temperature	51	13%	36	28%	43	18%
ES	Low-grade Fevers	52	13%	56	9%	55	9%
ES	Loss of Appetite/ Anorexia	53	13%	37	26%	46	16%
NS	**Metal Taste in Mouth**	54	13%	41	25%	30	26%
ES	Unexplained Weight Gain	55	13%	55	9%	49	14%
DS	Food intolerances (new)	56	13%	49	22%	37	21%
NS	**Headache (atypical/new onset)**	57	0%	19	44%	20	36%
NS	**Considered suicide/ suicidal ideation**	58	0%	43	24%	50	13%
CS	Hypertension (high blood pressure) (new onset)	59	0%	50	18%	51	13%
DS	Pain in Liver/Gallbladder Area	60	0%	47	22%	53	12%

* CS/Cardiovascular & Circulatory System; DS/Digestive System; ES/Endocrine System; IS/Integumentary System; **NS/Nervous System (bold)**; RS/Respiratory System; SS/Skeletal System; US/Urinary System

Total Respondents for each group 8 185 131

Table 14 – Comparison of Symptom Rankings to NSF Group shows the responses of the NSF Group listed from high to low percentages next to the ranking and response percentage for that symptom in the WITH and WITHOUT Groups.

In the NSF Group, multiple symptoms had the same reporting frequency. For comparison purposes, we included the 28 symptoms with a reporting frequency of 38% or higher. Symptoms that are ranked in the top 28 of the NSF Group and the WITH and/or WITHOUT Groups are highlighted in yellow in Table 14.

Note: The NSF Group consists of only 8 cases, and 6 of the 8 patients had their last MRI with contrast between 2003 and 2006 and may not have recalled all symptoms they experienced at that time.

Brain Fog & Cognitive Issues

In the literature, brain fog and cognitive issues are not usually identified as being symptoms of NSF. We believe we have found a possible explanation for it.

In a 2013 editorial in the "American Journal of Kidney Diseases", Seliger & Weiner opened with this first line - "*Cognitive impairment is common in individuals with chronic kidney disease (CKD), particularly among those treated with dialysis*."

Because cognitive impairment is common in patients on dialysis, any cognitive change in those patients may not have been recognized in case reports as also being a symptom of NSF. However, we know that gadolinium is neurotoxic (Mallio et al., 2020; Hui & Mullins, 2009; Ray et al., 1996).

Our Assessment: Skin changes and neuropathic symptoms not only predominate the early phase of NSF but also the symptoms experienced by survey participants. Of the top 28 symptoms in the NSF Group, 6 involve the skin and 14 the nervous system (NS); in addition, 2 involve the skeletal system, 2 the endocrine system, 2 the cardiovascular & circulatory system, 1 the digestive system, and 1 the respiratory system.

The WITH and WITHOUT Groups both had 19 of the same NSF symptoms in their top 28, and each group had 1 additional symptom for a total of 20 of the top 28 symptoms of the NSF Group.

The following 11 NS symptoms ranked in the top 28 of the NSF, WITH & WITHOUT Groups:

- Ache (dull continuous pain)
- Balance issues
- Brain fog/cognitive issues
- Burning pain
- Difficulty walking
- Dry eyes
- Low-level internal buzzing/electric-like sensations
- Muscle spasms/cramps
- Muscle twitching/fasciculations
- Numbness
- Tingling/prickling sensations

The other NS symptoms in the NSF Group's top 28 are dysphagia (swallowing problems), eye redness, and floaters (eyes).

The following 8 other symptoms are also in the top 28 of all three groups:

- Deep bone pain
- Digestive symptoms
- Fatigue
- Insomnia
- Itchy skin
- Pain in joints
- Shortness of breath
- Skin changes (hyperpigmented, mottled, or blotchy)

The results from the NSF Group may not carry much weight statistically due to the small size of the group. However, there are obvious similarities between the symptom rankings of the NSF Group and those of the WITH and WITHOUT Groups. The top 28 symptoms in the NSF Group are in line with the results of the WITH and WITHOUT Groups and the early-phase symptoms of NSF as described by Marckmann (Table 10). This similarity suggests that they are symptoms of Gd-induced NSF, or as Marckmann suggested calling it, Gd-induced systemic fibrosis.

Unconfounded Cases

Received the Same GBCA for all contrast MRIs

In the NSF-related literature, there was a focus on what were referred to as "unconfounded" cases. For consistency, we use the term here. Unconfounded NSF cases are those cases in which the patient received one dose of contrast or had multiple MRIs

with the same GBCA. Knowing which agent or type of agent was administered before the onset of symptoms can provide important information for researchers, and we are able to provide such information in Table 15.

Table 15. UNCONFOUNDED CASES
1 or More MRIs with Same Agent

Agent Received for All MRIs	WITH		WITHOUT	
	1 MRI	Multiple	1 MRI	Multiple
Ablavar®/Vasovist® (gadofosveset trisodium	0	0	0	0
Clariscan™ (gadoterate meglumine)	4	1	5	0
Dotarem® (gadoterate meglumine)	20	2	8	2
Elucirem™ (gadopiclenol)	0	0	0	0
Eovist® (gadoxetate disodium)	0	0	0	0
Gadovist® (gadobutrol)	16	8	3	3
Gadobutrol (generic, 2023)	0	0	0	0
Gadoterate Meglumine (generic, 2022)	0	0	0	0
Magnevist® (gadopentetate dimeglumine)	6	1	5	0
MultiHance® (gadobenate dimeglumine)	5	3	2	1
Omniscan™ (gadodiamide)	2	0	0	0
OptiMark™ (gadoversetamide)	2	0	0	0
Primovist® (gadoxetic acid disodium)	0	0	0	0
ProHance® (gadoteridol)	4	0	2	0
Vueway® (gadopiclenol)	1	0	0	0
Agent UNKNOWN – Had only 1 MRI	**9**	**0**	**19**	**0**
Unconfounded Cases – LINEAR	**15**	**4**	**7**	**1**
Unconfounded Cases – MACROCYCLIC	**45**	**11**	**18**	**5**
TOTAL UNCONFOUNDED CASES	**69**	**15**	**44**	**6**
	1 MRI	**Multiple**	**1 MRI**	**Multiple**

Symptoms Associated with Linear versus Macrocyclic Agents

Researchers have been looking for details that might link symptoms to linear versus macrocyclic agents (Tweedle, 2021). We provide that information for 75 Unconfounded Cases (19 linear & 56 macrocyclic) in the WITH Group. All patients have at least one test result that confirms they retained gadolinium longer than 30 days after their MRI, including as long as 14 years in pelvic bone and 13 years in sigmoid colon tissue (Table 3b). Symptom reporting frequencies and rankings within this group closely parallel those observed in the NSF Group and in the broader WITH cohort, reinforcing the consistency of the NSF-like symptom signature when agent identity is clearly defined and retention is documented.

In Table 17, the same 14 symptoms involving the nervous system ranked in the top 25 for linear & macrocyclic GBCAS:

Ache (dull continuous pain)	Headache (atypical/new onset)	Low-level internal buzzing/electric-like sensations
Balance issues	Lightheadedness/dizziness	Tingling/prickling sensations
Brain fog/cognitive issues	Muscle spasms/cramps	Tinnitus
Burning pain	Muscle twitching/fasciculations	Vision changes/blurry vision
Difficulty walking	Numbness	

7 other symptoms were in the top 25 for both types of GBCAs:

Deep bone pain	Fatigue	Pain in Joints	Skin changes (hyperpigmented, mottled or blotchy)
Digestive symptoms	Insomnia	Wrinkled skin	

For easier comparison, symptom responses from 75 Unconfounded Cases are presented here in two tables:

Table 16 – Symptom Reporting Frequency by Gender & Agent Type with symptoms in the order listed in the Survey. Response percentages for Females and Males are reported side-by-side for both linear and macrocyclic unconfounded cases.

Table 17 – Symptom Reporting Frequency Ranked from High to Low Percentages by Agent Type for 19 linear and 56 macrocyclic unconfounded cases in the WITH Group. All symptoms involving the nervous system are bold.

Table 16. SYMPTOMS / UNCONFOUNDED Cases / WITH Results			19 Linear Cases				56 Macrocyclic Cases			
Symptom Reporting Frequency by Gender & Agent Type for 75 Unconfounded Cases			14 Females		5 Males		37 Females		19 Males	
			#	%	#	%	#	%	#	%
1	**NS**	Ache (dull continuous pain)	9	64%	2	40%	20	54%	11	58%
2	**NS**	Burning pain	11	79%	4	80%	28	76%	11	58%
3	**NS**	Numbness	6	43%	3	60%	19	51%	7	37%
4	**NS**	Tingling / Prickling sensations	11	79%	2	40%	30	81%	14	74%
5	**NS**	Low-level internal buzzing / electric-like sensations	11	79%	1	20%	22	59%	8	42%
6	**NS**	Head Pain (stabbing/ sharp/ localized head pain)	6	43%	1	20%	21	57%	4	21%
7	**NS**	Headache (atypical/new onset)	7	50%	2	40%	17	46%	9	47%
8	**NS**	Brain Fog / Cognitive Issues	14	100%	4	80%	27	73%	6	32%
9	**NS**	Migraine Auras	2	14%	1	20%	7	19%	1	5%
10	**NS**	Lightheadedness/ Dizziness	8	57%	2	40%	21	57%	4	21%
11	**NS**	Seizures	1	7%	0	0%	3	8%	1	5%
12	**NS**	Considered suicide/ suicidal ideation	5	36%	1	20%	15	41%	2	11%
13	**NS**	Muscle Spasms/ Cramps	9	64%	3	60%	15	41%	7	37%
14	**NS**	Muscle Twitching / Fasciculations	9	64%	4	80%	25	68%	10	53%
15	**NS**	Balance Issues	8	57%	2	40%	15	41%	4	21%
16	**NS**	Difficulty Walking	6	43%	2	40%	14	38%	5	26%
17	SS	Deep Bone Pain	12	86%	2	40%	19	51%	7	37%
18	SS	Pain in Joints	11	79%	3	60%	20	54%	8	42%
19	SS	Joint instability (clicking, popping, unstable joints)	5	36%	2	40%	12	32%	5	26%
20	SS	Pain in Ribs	9	64%	1	20%	10	27%	6	32%
21	IS	Skin Changes (hyperpigmented, mottled, or blotchy)	8	57%	4	80%	16	43%	3	16%
22	IS	Skin Rash	7	50%	3	60%	10	27%	5	26%
23	IS	Skin Lesions (such as ulcers, papules, macules, or nodules)	5	36%	2	40%	8	22%	2	11%
24	IS	Wrinkled skin (accelerated aging of skin)	6	43%	2	40%	18	49%	7	37%
25	IS	Itchy Skin	6	43%	2	40%	11	30%	6	32%
26	IS	Tight Skin	7	50%	1	20%	9	24%	3	16%
27	IS	Stretchy Skin	1	7%	1	20%	0	0%	0	0%
28	IS	Sagging Skin	1	7%	1	20%	8	22%	1	5%
29	CS	Hypotension (low blood pressure) (new onset)	1	7%	0	0%	9	24%	1	5%
30	CS	Hypertension (high blood pressure) (new onset)	1	7%	1	20%	4	11%	1	5%
31	CS	Labile Hypertension	1	7%	0	0%	1	3%	0	0%
32	CS	Tachycardia (fast heart rate)	3	21%	1	20%	19	51%	5	26%
33	CS	Arrhythmias (irregular heartbeat)	5	36%	1	20%	11	30%	5	26%
34	CS	Other Palpitations	3	21%	1	20%	9	24%	4	21%
35	CS	Chest Pain	5	36%	1	20%	12	32%	5	26%
36	RS	Shortness of Breath	3	21%	1	20%	14	38%	3	16%
37	CS	Edema (swelling of extremities)	2	14%	1	20%	2	5%	1	5%
38	DS	Digestive Symptoms (nausea, vomiting, diarrhea, constipation, etc)	10	71%	3	60%	19	51%	6	32%
39	DS	Abdominal Pain	6	43%	1	20%	12	32%	6	32%
40	US	Pain in Kidneys or Bladder	3	21%	1	20%	13	35%	7	37%
41	DS	Pain in Liver/Gallbladder Area	3	21%	0	0%	6	16%	5	26%
42	**NS**	Dysphagia (swallowing problems)	4	29%	1	20%	6	16%	3	16%
43	**NS**	Speech Difficulty/ Voice Changes	4	29%	3	60%	9	24%	3	16%
44	**NS**	Eye Redness	3	21%	1	20%	10	27%	4	21%
45	**NS**	Dry Eyes	6	43%	1	20%	18	49%	9	47%
46	**NS**	Floaters (eyes)	5	36%	2	40%	10	27%	6	32%
47	**NS**	Vision Changes / Blurry Vision	8	57%	3	60%	16	43%	9	47%
48	**NS**	Tinnitus (ringing in ears)	7	50%	1	20%	19	51%	6	32%
49	ES	Hair Loss	7	50%	2	40%	12	32%	6	32%
50	ES	Low Body Temperature	1	7%	0	0%	13	35%	4	21%
51	ES	Low-grade Fevers	1	7%	0	0%	3	8%	1	5%
52	ES	Fatigue	10	71%	2	40%	27	73%	8	42%
53	ES	Insomnia	7	50%	3	60%	23	62%	7	37%
54	ES	Loss of Appetite/ Anorexia	2	14%	2	40%	11	30%	2	11%
55	**NS**	Loss of Taste	2	14%	0	0%	4	11%	1	5%
56	RS	Flu-like Symptoms	4	29%	0	0%	11	30%	1	5%
57	**NS**	Metal Taste in Mouth	5	36%	1	20%	7	19%	4	21%
58	ES	Unexplained Weight Loss	3	21%	1	20%	12	32%	5	26%
59	ES	Unexplained Weight Gain	2	14%	0	0%	4	11%	1	5%
60	DS	Food intolerances (new)	3	21%	0	0%	9	24%	3	16%

* CS/Cardiovascular & Circulatory System; DS/Digestive System; ES/Endocrine System; IS/Integumentary System; **NS/Nervous System (bold);** RS/Respiratory System; SS/Skeletal System; US/Urinary System

Total by Gender & Agent Type: Female (F) & Male (M) **14 F/Linear** **5 M/Linear** **37 F/Macro** **19 M/Macro**

Table 17. SYMPTOMS / 75 UNCONFOUNDED Cases / WITH Results Group

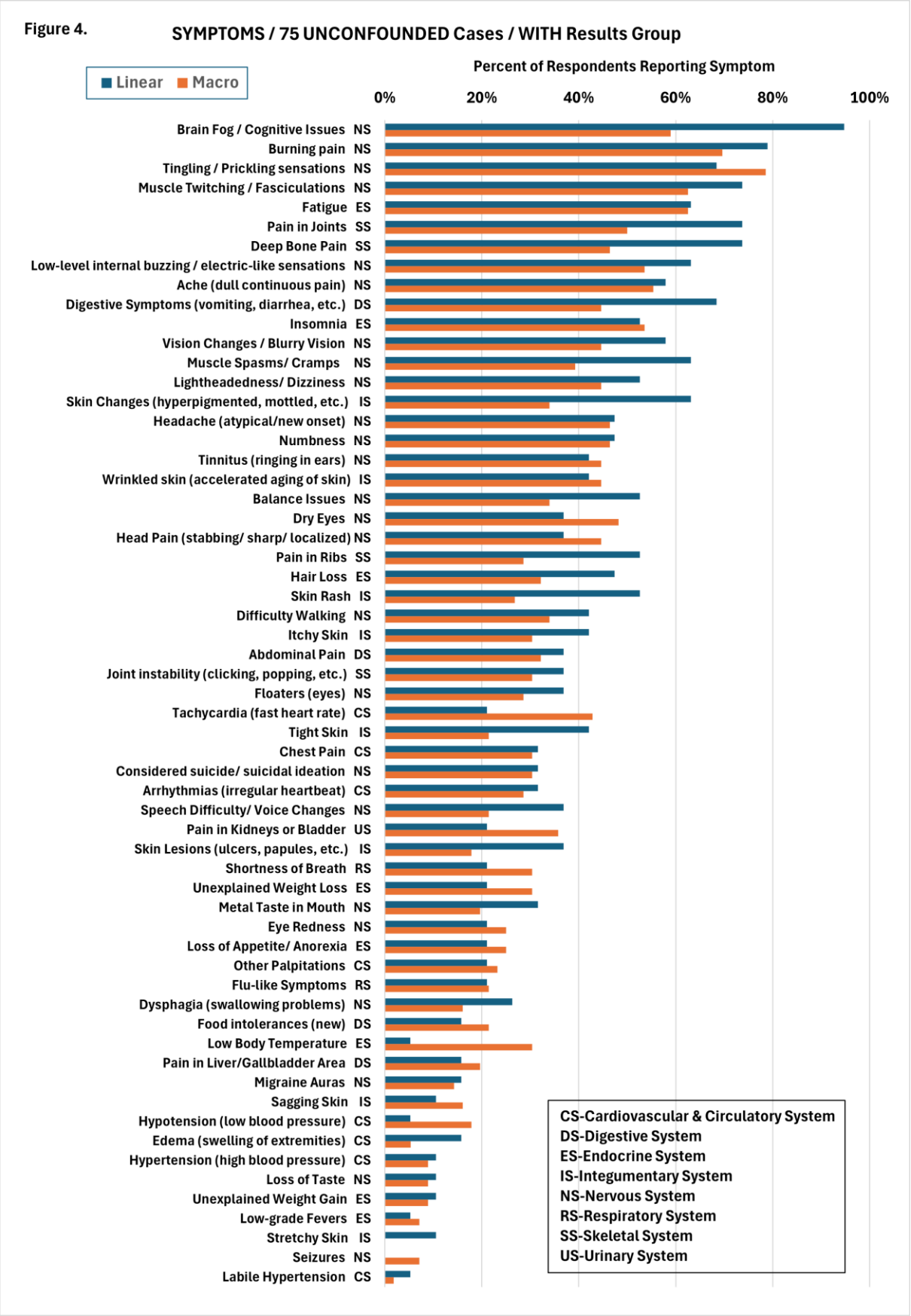
Percentages Calculated on Total Unconfounded Cases by Agent Type

	(Responses sorted from high to low percentages)		19 LINEAR #	19 LINEAR %		(Responses sorted from high to low percentages)	56 MACRO #	56 MACRO %
1	*NS	**Brain Fog / Cognitive Issues**	**18**	**95%**	**NS**	**Tingling / Prickling sensations**	**44**	**79%**
2	**NS**	**Burning pain**	**15**	**79%**	**NS**	**Burning pain**	**39**	**70%**
3	SS	Deep Bone Pain	14	74%	**NS**	**Muscle Twitching / Fasciculations**	**35**	**63%**
4	SS	Pain in Joints	14	74%	ES	Fatigue	35	63%
5	**NS**	**Tingling / Prickling sensations**	**13**	**68%**	**NS**	**Brain Fog / Cognitive Issues**	**33**	**59%**
6	**NS**	**Muscle Twitching / Fasciculations**	**13**	**68%**	**NS**	**Ache (dull continuous pain)**	**31**	**55%**
7	DS	Digestive Symptoms (nausea, vomiting, diarrhea, etc.)	13	68%	**NS**	**Low-level internal buzzing / electric-like sensations**	**30**	**54%**
8	**NS**	**Low-level internal buzzing / electric-like sensations**	**12**	**63%**	ES	Insomnia	30	54%
9	**NS**	**Muscle Spasms/ Cramps**	**12**	**63%**	SS	Pain in Joints	28	50%
10	IS	Skin Changes (hyperpigmented, mottled, or blotchy)	12	63%	**NS**	**Dry Eyes**	**27**	**48%**
11	ES	Fatigue	12	63%	**NS**	**Numbness**	**26**	**46%**
12	**NS**	**Ache (dull continuous pain)**	**11**	**58%**	**NS**	**Headache (atypical/new onset)**	**26**	**46%**
13	**NS**	**Vision Changes / Blurry Vision**	**11**	**58%**	SS	Deep Bone Pain	26	46%
14	**NS**	**Lightheadedness/ Dizziness**	**10**	**53%**	**NS**	**Head Pain (stabbing/ sharp/ localized head pain)**	**25**	**45%**
15	**NS**	**Balance Issues**	**10**	**53%**	**NS**	**Lightheadedness/ Dizziness**	**25**	**45%**
16	SS	Pain in Ribs	10	53%	IS	Wrinkled skin (accelerated aging of skin)	25	45%
17	IS	Skin Rash	10	53%	DS	Digestive Symptoms (nausea, vomiting, diarrhea, etc.)	25	45%
18	ES	Insomnia	10	53%	**NS**	**Vision Changes / Blurry Vision**	**25**	**45%**
19	**NS**	**Numbness**	**9**	**47%**	**NS**	**Tinnitus (ringing in ears)**	**25**	**45%**
20	**NS**	**Headache (atypical/new onset)**	**9**	**47%**	CS	Tachycardia (fast heart rate)	24	43%
21	ES	Hair Loss	9	47%	**NS**	**Muscle Spasms/ Cramps**	**22**	**39%**
22	**NS**	**Difficulty Walking**	**8**	**42%**	US	Pain in Kidneys or Bladder	20	36%
23	IS	Wrinkled skin (accelerated aging of skin)	8	42%	**NS**	**Balance Issues**	**19**	**34%**
24	IS	Itchy Skin	8	42%	**NS**	**Difficulty Walking**	**19**	**34%**
25	**NS**	**Tinnitus (ringing in ears)**	**8**	**42%**	IS	Skin Changes (hyperpigmented, mottled, or blotchy)	19	34%
26	IS	Tight Skin	8	42%	DS	Abdominal Pain	18	32%
27	**NS**	**Head Pain (stabbing/ sharp/ localized head pain)**	**7**	**37%**	ES	Hair Loss	18	32%
28	SS	Joint instability (clicking, popping, unstable joints)	7	37%	**NS**	**Considered suicide/ suicidal ideation**	**17**	**30%**
29	IS	Skin Lesions (such as ulcers, papules, macules, or nodule	7	37%	SS	Joint instability (clicking, popping, unstable joints)	17	30%
30	DS	Abdominal Pain	7	37%	IS	Itchy Skin	17	30%
31	**NS**	**Speech Difficulty/ Voice Changes**	**7**	**37%**	CS	Chest Pain	17	30%
32	**NS**	**Dry Eyes**	**7**	**37%**	RS	Shortness of Breath	17	30%
33	**NS**	**Floaters (eyes)**	**7**	**37%**	ES	Low Body Temperature	17	30%
34	**NS**	**Considered suicide/ suicidal ideation**	**6**	**32%**	ES	Unexplained Weight Loss	17	30%
35	CS	Arrhythmias (irregular heartbeat)	6	32%	SS	Pain in Ribs	16	29%
36	CS	Chest Pain	6	32%	CS	Arrhythmias (irregular heartbeat)	16	29%
37	**NS**	**Metal Taste in Mouth**	**6**	**32%**	**NS**	**Floaters (eyes)**	**16**	**29%**
38	**NS**	**Dysphagia (swallowing problems)**	**5**	**26%**	IS	Skin Rash	15	27%
39	CS	Tachycardia (fast heart rate)	4	21%	**NS**	**Eye Redness**	**14**	**25%**
40	CS	Other Palpitations	4	21%	ES	Loss of Appetite/ Anorexia	14	25%
41	RS	Shortness of Breath	4	21%	CS	Other Palpitations	13	23%
42	US	Pain in Kidneys or Bladder	4	21%	IS	Tight Skin	12	21%
43	**NS**	**Eye Redness**	**4**	**21%**	**NS**	**Speech Difficulty/ Voice Changes**	**12**	**21%**
44	ES	Loss of Appetite/ Anorexia	4	21%	RS	Flu-like Symptoms	12	21%
45	RS	Flu-like Symptoms	4	21%	DS	Food intolerances (new)	12	21%
46	ES	Unexplained Weight Loss	4	21%	DS	Pain in Liver/Gallbladder Area	11	20%
47	**NS**	**Migraine Auras**	**3**	**16%**	**NS**	**Metal Taste in Mouth**	**11**	**20%**
48	CS	Edema (swelling of extremities)	3	16%	IS	Skin Lesions (such as ulcers, papules, macules, or nodule	10	18%
49	DS	Pain in Liver/Gallbladder Area	3	16%	CS	Hypotension (low blood pressure) (new onset)	10	18%
50	DS	Food intolerances (new)	3	16%	IS	Sagging Skin	9	16%
51	IS	Stretchy Skin	2	11%	**NS**	**Dysphagia (swallowing problems)**	**9**	**16%**
52	IS	Sagging Skin	2	11%	**NS**	**Migraine Auras**	**8**	**14%**
53	CS	Hypertension (high blood pressure) (new onset)	2	11%	CS	Hypertension (high blood pressure) (new onset)	5	9%
54	**NS**	**Loss of Taste**	**2**	**11%**	**NS**	**Loss of Taste**	**5**	**9%**
55	ES	Unexplained Weight Gain	2	11%	ES	Unexplained Weight Gain	5	9%
56	CS	Hypotension (low blood pressure) (new onset)	1	5%	**NS**	**Seizures**	**4**	**7%**
57	CS	Labile Hypertension	1	5%	ES	Low-grade Fevers	4	7%
58	ES	Low Body Temperature	1	5%	CS	Edema (swelling of extremities)	3	5%
59	ES	Low-grade Fevers	1	5%	CS	Labile Hypertension	1	2%
60	**NS**	**Seizures**	**1**	**5%**	IS	Stretchy Skin	0	0%

* CS/Cardiovascular & Circulatory System; DS/Digestive System; ES/Endocrine System; IS/Integumentary System; **NS/Nervous System (bold)**; RS/Respiratory System; SS/Skeletal System; US/Urinary System

Unconfounded Cases with LINEAR Agent 19 **Unconfounded Cases with MACROCYCLIC Agent 56**

Figure 4 below provides a different perspective of the symptoms data presented in Table 17.



Chronic Adverse Effects

The symptoms data presented in the previous tables appears to indicate that the nervous system may be the body system most affected by gadolinium, which could potentially result in a cascade of adverse effects.

Although the cause has not been confirmed, many survey respondents indicated that their initial symptoms became chronic or progressive, resulting in new diagnoses, functional disabilities or limitations, and reduced quality of life.

New Diagnoses / Autoimmune Diseases or Other Health Conditions

Patients were asked if they had been diagnosed with an autoimmune disease or other health condition that they believe relates to the signs or symptoms they identified elsewhere in the questionnaire.

71 (38%) of the patients in the WITH Group and 42 (32%) in the WITHOUT Group indicated they had received a new diagnosis since their last contrast MRI. The complete list of new diagnoses can be found in Appendix 2.

Patients in the WITH and WITHOUT Groups reported the following new diagnoses multiple times:

Fibromyalgia (13 cases)
Hashimoto's & Hypothyroidism (10 cases)
Mast Cell Activation Syndrome (MCAS) (7 cases)
Small Fiber Neuropathy (SFN) (6 cases)
Cognitive deficits/Functional cognitive disorder/Dementia (5 cases)

While causality cannot yet be established, biological plausibility is present: gadolinium has been shown to excite pro-inflammatory cytokines (Maecker et., 2020), activate mast cells (Liu et al., 2022; Garcia-Bara et al., 2022), disrupt mitochondrial function (Goetzl et al., 2022, and trigger oxidative stress and inflammatory pathways (Coimbra., 2024). These are all mechanisms implicated in autoimmune and inflammatory disease pathogenesis.

In addition, prior studies suggest plausible associations between GBCA exposure and the conditions listed above. Fibromyalgia-like symptoms have been reported after repeated GBCA exposure (Lattanzio & Imbesi, 2020; Lattanzio, 2019), and preclinical studies indicate that gadolinium deposition in tissues may affect small nerve fibers, potentially contributing to SFN (Krämer et al., 2023; Radbruch et al., 2020). Gadolinium has also been implicated in mast cell activation, suggesting a possible mechanistic link to MCAS-like symptoms in susceptible individuals (Ruiz de Azcárate, et al., 2023; Garcia-Bara et al., 2022; Liu et al., 2022). Experimental studies further indicate that GBCA exposure may disrupt thyroid hormone receptor function, which could be relevant for new-onset Hashimoto's disease or hypothyroidism (Ariyani et al., 2016; Kartamihardja et al., 2021). In the context of cognitive function, animal and imaging studies demonstrate gadolinium accumulation in the central nervous system, though clinical evidence for long-term cognitive deficits remains limited (Yao et al., 2024; Iyad et al., 2023; Khairinisa et al., 2021). Collectively, these findings underscore the need for further systematic investigation into potential immune, neuroimmune, and endocrine sequelae following GBCA exposure. These observations highlight that gadolinium-based contrast agents, administered intravenously, circulate throughout the body and can interact with multiple organ systems. This systemic exposure may be linked to multi-organ and immune-related effects, emphasizing the need for further research to better understand the spectrum and mechanisms of GBCA-related outcomes.

Functional Disabilities & Other Limitations

Patients were asked about post-contrast MRI events that caused them to become disabled or to suffer functional disabilities that adversely affected their quality of life. There was no time limit as to when these events occurred. Patients were instructed to select only those events that occurred since their last dose of a GBCA.

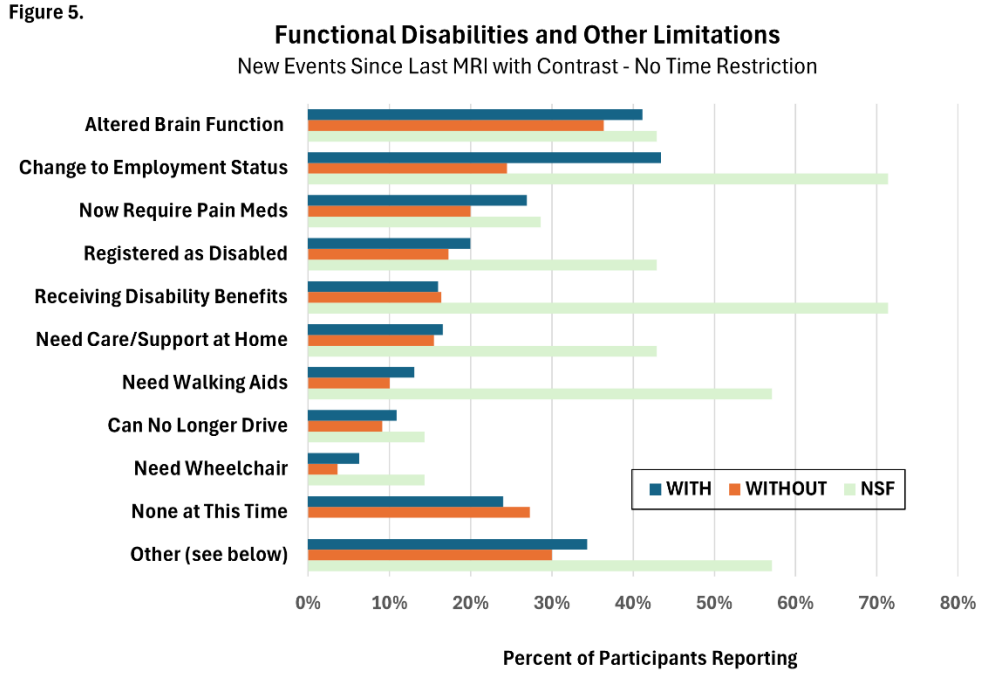
Altered Brain Function and Change to Employment Status affected more patients in our survey:

43% (76/175) in the WITH Group and 25% (27/110) in the WITHOUT Group indicated they had a change in their employment status due to their health issues, reduced working hours, and loss of income.

41% (72/175) in the WITH Group and 36% (40/110) in the WITHOUT Group said their altered brain function and memory affects their ability to work as they did prior to the MRIs with a GBCA.

The complete results are presented in Figure 5 below.

Figure 5.



Other Issues affecting Patients' Quality of Life

The other comments made by patients shed light on the scope of the life-altering effects of retained gadolinium. Some health issues were mentioned multiple times, particularly those involving muscles, bone pain, spine, fatigue, neurological issues, and pain in general. Some people reported losing their job or business. One person had to drop out of high school; another had to reduce their course load in college and needed text-to-speech reading aids. Several people mentioned being bedridden or homebound. The comments of these patients (and others) suggest that retained gadolinium can have long-term adverse effects.

Current Status of Symptoms & What Helped

Respondents were provided with a list and asked to select which answer choice best described the current status of their symptoms that they believe were caused by retained gadolinium.

As Table 17 shows, 32 patients in the WITH Group and 15 in the WITHOUT Group reported at least 75% improvement in their symptoms. However, 39 patients in the WITH Group and 32 in the WITHOUT Group said they had no improvement at all.

There were 88 patients in the WITH and WITHOUT Groups who reported that some of their symptoms have improved but others have gotten worse. The list of symptoms patients said have worsened or continued can be found in Appendix 3.

On a positive note, 1 person in the NSF Group reported a 75% improvement in their symptoms, which was unexpected.

Table 17. Current Status of Symptoms

Answer Choices	WITH		WITHOUT		NSF	
I have had no improvement in my symptoms.	39	23%	32	29%	2	29%
I have had 25% or mild improvement in my symptoms.	20	12%	15	14%	0	0%
I have had 50% or modest improvement in my symptoms.	23	13%	17	16%	0	0%
I have had 75% or good to very good improvement.	26	15%	10	9%	1	14%
I am now completely or nearly completely symptom free.	6	4%	5	5%	0	0%
I am now totally disabled	-	-	-	-	2	29%
Some symptoms improved but others have gotten worse.	58	34%	30	28%	2	29%
Total Answered	**172**		**109**		**7**	

Table 18. What Contributed to Symptom Improvement

Answer Choices / Select all that apply	WITH		WITHOUT		NSF	
My symptoms have not improved.	39	23%	32	29%	4	57%
Time (natural progression of improvement)	80	47%	52	48%	1	14%
IV chelation therapy with DTPA	35	20%	2	2%	0	0%
IV chelation therapy with EDTA	10	6%	0	0%	0	0%
Oral EDTA	4	2%	3	3%	0	0%
Sauna therapy	37	22%	12	11%	0	0%
Dietary changes	55	32%	33	30%	1	14%
Physical exercise	50	29%	23	21%	2	29%
Alternative therapies (e.g., acupuncture, homeopathy)	45	26%	27	25%	0	0%
Other treatments, medications, or supplements	78	45%	43	39%	4	57%
Total Answered	**172**		**109**		**7**	

Patients with Significant Improvement

In response to anticipated questions, we are providing details of the GBCA history of the patients with 75% to 100% improvement. The type and frequency of GBCA exposure does not appear to explain improvement of their symptoms.

100% Improvement WITH Group:
5 had 1 MRI - 2 with Gadovist; 1 MultiHance; 1 Omniscan; 1 with unknown agent.
1 had 5 MRIs with Gadovist

100% Improvement WITHOUT Group:
4 had 1 MRI – 1 with Clariscan; 1 MultiHance; 2 with unknown agent.
1 had between 6 & 10 MRIs with unknown agents.

75% Improvement WITH Group:
13 had 1 MRI – 4 with Dotarem; 1 Eovist; 2 Gadovist; 3 Magnevist; 2 MultiHance; 1 OptiMark.
6 had 2 MRIs – 1 Dotarem confounded case; 2 Gadovist unconfounded; 1 Gadovist confounded; 2 ProHance confounded.
1 had 5 MRIs & last was with Dotarem.
2 had between 6 & 10 MRIs – last with Magnevist (1); unknown agent (1).
1 had 9 MRIs – last with Magnevist.
1 had between 11 & 15 MRIs – last with Gadovist.
2 Do not know how many MRIs they had, but last agent received was Dotarem (1) & Clariscan (1).

75% Improvement WITHOUT Group:
2 had 1 MRI with Dotarem.
2 had 2 MRs – 1 with MultiHance; 1 with unknown agent(s).
2 had 4 MRIs with unknown agent(s).
2 had 5 MRIs with unknown agent(s).
1 had between 6 & 10 MRIs with unknown agent(s).
1 had more than 20 MRIs & last agent received was Gadovist.

75% Improvement NSF Group: 1 person had 6 MRIs with Omniscan within 3 weeks.

Treatment Information

Details of various other treatments, supplements, or detoxification methods mentioned by survey respondents are not being provided in this report. However, we provide the following treatment information for those with 75% to 100% improvement.

Based on the percentage of responses in Table 18, which includes the results below, it appears that time, dietary changes and physical exercise may provide some level of relief for some patients who have been affected by gadolinium.

Treatments & number of responses for the 11 patients in the 100% Improvement WITH & WITHOUT Groups:

Time (natural progression of improvement) (9)	Sauna therapy (0)
IV chelation with DTPA (1)	Dietary changes (4)
IV chelation with EDTA (1)	Physical exercise (2)
Oral EDTA (0)	Alternative therapies (e.g., acupuncture, homeopathy) (1)

Treatments & number of responses for the 36 patients in the 75% Improvement WITH & WITHOUT Groups

Time (natural progression of improvement) (24)	Sauna therapy (10)
IV chelation with DTPA (5)	Dietary changes (20)
IV chelation with EDTA (1)	Physical exercise (13)
Oral EDTA (2)	Alternative therapies (e.g., acupuncture, homeopathy) (10)

75% Improvement NSF Group:
The NSF patient attributed their improvement to "extreme self-therapy, exercise, swimming, walking, and lifting very light weights." Although having 75% improvement, that individual still has issues with range of motion, flexibility, stiff joints, weak joints on fingers, restricted flexibility in their wrist, and their ligaments and tendons have never recovered.

Troubling Survey Responses

Told symptoms psychosomatic – Many patients shared that their doctors dismissed their concerns that the symptoms they were experiencing were caused by the GBCA or gadolinium. Patients' concerns were not only dismissed, but many doctors told the patient their symptoms were psychosomatic or caused by mental or emotional disturbances. This troublesome occurrence was reported by 60% of the WITH Group, 47% of the WITHOUT Group, and 38 % of the NSF group.

Clinicians should be better informed about the issue of Gd retention and made aware that *everyone* can retain some gadolinium from each contrast MRI, and it could cause symptoms in some people. The lack of recognition of their symptoms can have a negative impact on patients' mental health.

Considered suicide – Another concerning statistic is that 45 patients (24%) in the WITH Group, and 17 patients (13%) in the WITHOUT Group indicated they had considered suicide. Those are troubling numbers that should not be ignored or accepted as just being another potential side effect of having an MRI with contrast. Study authors are aware of cases in which affected individuals have taken their own lives.

Respondents described a devastating loss of independence, function, career, and social connections, often compounded by limited clinical recognition of their symptoms. Such experiences can lead to isolation, hopelessness, and self-blame. Suicidal ideation in this context may arise from the combined effects of persistent, debilitating symptoms, possible neurotoxic mechanisms, and the psychological burden of medical dismissal. This issue merits further regulatory attention and greater clinical awareness to ensure that patients receive appropriate support and follow-up care.

DISCUSSION

When we began this project, our goal was not to prove how or why gadolinium exposure might cause the symptoms reported by patients, but to carefully document the results. As the data was reviewed, consistent and biologically plausible patterns became apparent, prompting consideration of how these findings relate to established clinical observations. We believe it is important to point out how the results of this Patient Survey relate to the clinical picture of NSF and how gadolinium's toxic effects, particularly on calcium channels and the nervous system, may explain many of the symptoms experienced by both NSF patients and those with normal renal function.

It is widely recognized that retained gadolinium is the primary cause of NSF in renally impaired patients. The question now is whether retained gadolinium can cause harm to patients with normal renal function when it is retained in varying quantities, in different body systems, and for potentially long periods of time, regardless of the patient's level of renal function.

Symptoms of NSF & Gd Toxicity

For this Patient Survey, we wanted to know how the clinical picture of NSF might compare to participants' responses to our questions about Signs & Symptoms after gadolinium administration. Marckmann & Skov's 2009 paper, "*Nephrogenic Systemic Fibrosis: Clinical Picture and Treatment*", and Marckmann, 2011, provide important clinical details about NSF that may not be widely known, such as the observation that "*skin changes and neuropathic symptoms predominate the early phase of NSF.*"

Table 10 provides details about the clinical picture of NSF, and the symptoms data in Tables 12 and 13 indicates that neuropathic symptoms predominate the early phase of the symptoms reported by patients with normal renal function as well.

According to other details provided by Marckmann (2009 & 2011), there were significant individual differences in the clinical course of NSF, even in ESRD patients, which seems to indicate that retained gadolinium could trigger a range of symptoms, with a varied clinical outcome in all patient populations.

The variability of the symptoms was likely due to many factors, but it shows that even in severely renally impaired patients Gd-induced NSF did not cause the exact same set of symptoms or level of severity; in other words, it was a disease of degrees.

The hallmark signs of the late stages of NSF are skin changes and contractures, but Marckmann wrote there were "other GBCA-associated symptoms that have not received the same attention but still may be considered part of the NSF syndrome." He added, "The other late manifestations of NSF can have a marked impact on the life quality of the patient." The results in Figure 5 about functional disabilities and limitations indicate this is the case for patients with normal renal function as well.

We believe the variability in the severity of symptoms seen with NSF (Table 11) explains what is currently happening to patients with normal renal function. These patients are experiencing many of the same symptoms as those with NSF, but for the most part, few of them develop NSF-like skin changes, and those who do have difficulty obtaining skin biopsies.

Without *visible* evidence of a problem, patients with normal renal function are less likely to have their cases investigated for a connection to gadolinium, so there is no gadolinium-related diagnosis or reporting to the FDA. As a result, the full scope of the adverse health effects caused by retained gadolinium may remain unrecognized, at least until non-visible manifestations are formally acknowledged and patients gain access to appropriate diagnostic evaluation.

Gd, Calcium Channels & the Nervous System

Symptom results for both the NSF and normal renal function groups confirm that the nervous system is significantly affected by gadolinium with 14 to 16 of each group's top 25 symptoms involving the nervous system (Tables 13 & 14). For the unconfounded cases, 14 of the same nervous system symptoms ranked in the top 25 for cases involving both linear and macrocyclic agents (Table 17).

Some symptoms could be caused by the gadolinium ion (Gd^{3+}) competing with calcium (Ca^{2+}) in all biological systems that require calcium for proper function (Sherry et al., 2009). Calcium ions control all cellular processes not only by generating electrical signals but also by functioning as signaling molecules (Kloc et al., 2025).

Besides competing with calcium, gadolinium could cause symptoms via its direct access to the sensory neurons in the dorsal root ganglion (DRG) (Godel et al., 2016). A 2014 study found that "gadolinium can directly activate a large population of human nociceptive DRG neurons" (Zhang et al., 2014). The DRG contains the greatest proportion of the body's sensory neurons, cells that transmit information to the central nervous system (CNS) (Krames, 2014). We know that almost immediately after GBCA administration, it gains access to the patient's cerebrospinal fluid (CSF) and CNS, including in patients with an intact blood-brain barrier (Nehra et al., 2018; Berger et al., 2018).

In 2017, McDonald et al., wrote that the discovery of neuronal tissue deposition of Gd, including *within* the nucleus of a neuronal cell, "raises the possibility of biologic activity of these deposits, possibly from modulation of calcium channel activity or direct interaction with cellular biomolecules."

A 2024 review article provides data gathered from 93 studies on the toxicity mechanisms of gadolinium and GBCAs. Some of the identified toxicity mechanisms involve signaling pathways; upregulation of inflammation, oxidative stress and apoptosis; and promoting production of reactive oxygen species (ROS). Gadolinium was found to interfere with calcium homeostasis. The authors found that competition of Gd^{3+} with calcium, needed for cellular processes, was highlighted as a potential mechanism of cytotoxicity in several studies (Coimbra et al., 2024).

Evidence of Harm

Evidence suggesting potential mechanisms of harm extends beyond what is visible to the naked eye or seen under a microscope: body systems may *dysfunction* when gadolinium interferes with various processes, particularly those that require calcium for proper function. Gadolinium's interference with calcium channels has been shown to affect mitochondrial function in the nervous system (Goetzl et al., 2022), which plays a critical role in the functioning of human body systems. Gadolinium has also been shown to excite pro-inflammatory cytokines (Maecker et al., 2020), representing another possible pathway to symptom development.

The discovery of gadolinium-rich nanoparticles was first reported in 2016 (Wagner et al., 2016; Wagner, 2017). Research since then has revealed the *in vivo* toxicity of insoluble gadolinium-rich nanoparticles evidenced by mitochondrial swelling, cristae disruption, renal proximal tubular epithelial lysis, and pathological endosomal structures (Henderson et al., 2025; Cunningham et al., 2024; Do et al., 2020; Do et al., 2019). Accumulation of gadolinium-rich nanoparticles *inside* cells could potentially cause chronic metallosis, even in patients with normal kidney function (DeAguero et al., 2023).

The works cited in this paper are part of a growing body of research that identifies the toxic effects of gadolinium and GBCAs. Moreover, there is also confirmation of these effects in the 2007 FDA, Division of Medical Imaging and Hematology Products, "Memorandum to the File", from Medical Reviewer, Melanie Blank, MD. The topic was: Gadolinium-Based Contrast Agents (GBCAs) and Nephrogenic Systemic Fibrosis (NSF), Date Completed: 5/15/07 (Appendix 4). Item 'b' in the Summary states the following: *"Unchelated gadolinium is a very toxic compound, particularly to the liver and to calcium channels."*

The FDA's recognition that gadolinium is toxic to calcium channels is important. However, the FDA should have recognized that its toxic effect on calcium channels is also how gadolinium can cause harm. We believe gadolinium's documented adverse effects on the *function* of cells, particularly nerve cells that require calcium for proper function, provides evidence of how some and perhaps all patients can be harmed. It could well explain many of the 'unexplained' symptoms experienced by survey participants and other patients after their MRIs with a GBCA.

Retained Gd is Not Benign

Since the initial clinical experience with Gd-DTPA in 1984 (Carr et al.), extensive research has documented gadolinium retention in patients with normal renal function. Framing this retention as biologically inert is increasingly difficult to reconcile with mechanistic studies indicating that gadolinium-based contrast agents can disrupt mitochondrial and cellular processes. This dissonance between evidence and interpretation highlights the need for renewed scientific scrutiny. In light of emerging patient-reported and mechanistic findings, the data presented here invite a re-examination of prevailing assumptions about retained gadolinium.

We have the results of this Patient Survey with 316 patients with normal and near normal renal function reporting symptoms involving multiple body systems soon after their MRIs with a GBCA. Of these, 185 have one or more test results that confirm gadolinium retention for as long as 22 years after contrast administration, including in bone for more than 14 years from one dose of a linear GBCA and 4 years from one dose of a macrocyclic GBCA.

While many of the reported symptoms (e.g., fatigue, paresthesia) are nonspecific, the consistent clustering of neuropathic and calcium-related manifestations across the patient groups strengthens the plausibility of a shared mechanism, which in this case is gadolinium.

The survey results, combined with two-biopsy confirmed NSF diagnoses in patients with normal renal function, including one diagnosed in 2024 after exposure to macrocyclic agents, provide compelling evidence that challenges the assumption that retained gadolinium is clinically benign in patients with normal renal function. These findings warrant urgent investigation into the biological activity of retained gadolinium across all patient populations.

A Disease of Degrees

During the FDA's 2017 MIDAC public meeting on gadolinium retention, Williams and Grimm (The Lighthouse Project) described gadolinium toxicity as a "disease of degrees," with NSF representing its most severe manifestation. Highlighting this statement, the findings of this Patient Survey, together with existing clinical and mechanistic evidence, challenge the current binary view of gadolinium-induced disease as either "nephrogenic systemic fibrosis (NSF)" or "no effect." Current medical guidance and regulatory frameworks largely recognize harm only in the context of NSF, often dismissing gadolinium retention in patients with normal renal function as clinically insignificant. The findings in this survey, however, point to a spectrum of toxicity in which severity and organ involvement can vary among individuals. Across all patient groups, the most frequently reported manifestations involved the nervous, musculoskeletal, and integumentary systems. This pattern mirrors the early neuropathic and inflammatory phases of NSF as described by Marckmann and Skov (2009) and by Mendoza and colleagues (2006).

Marckmann (2009) observed that some GBCA-exposed patients developed early-phase symptoms of NSF without progressing to the late fibrosing form, which he termed "abortive or subclinical NSF." The symptom clusters identified in this survey extend that observation to patients without renal impairment. This suggests that the difference between "NSF" and "non-NSF" may be one of severity rather than kind, supporting the interpretation that gadolinium toxicity represents a spectrum of biological injury rather than an all-or-nothing phenomenon, where organ involvement and reversibility vary among individuals. While we cannot establish causation yet, the consistency and coherence of the reported symptom patterns represent an

emerging safety signal that warrants careful attention. Recognizing gadolinium-related disease as a possible spectrum of manifestations, rather than a rare, binary condition, may help the medical community strengthen patient safety, refine risk assessment, and prioritize further investigation into the mechanisms and true scope of gadolinium-associated effects.

One may ask: Is NSF itself the "disease of degrees"? Do all patients affected by gadolinium manifest NSF to varying extents, but without the "N" or nephrogenic component" The many similarities between the early clinical picture of NSF and the symptoms reported by participants in this Patient Survey suggest that they do.

ONE Disease with Varying Severity

Gadolinium Deposition Disease (GDD) is a term introduced by Semelka and colleagues (2016, refined in 2023) to describe a range of symptoms reported by patients with normal renal function following exposure to gadolinium-based contrast agents (GBCAs). These individuals often experience symptoms (as listed below) that resemble, and are generally less severe than, those observed in NSF. The concept of GDD was introduced to describe cases of gadolinium toxicity occurring in patients without significant kidney disease, thereby expanding the diagnostic framework beyond its traditional association with NSF.

However, our findings suggest that GDD and NSF may not represent separate disease entities. Instead, they are likely to reflect different points along a continuum of gadolinium-induced toxicity. In other words, what we are observing may be ONE gadolinium-induced disease process manifesting with varying degrees of severity, as Marckmann originally described NSF in his Severity Grading (See Table 11, NSF Severity Grading).

The severity of Gd-induced symptoms may depend on multiple factors, including the amount of gadolinium retained (which may be cumulative; McDonald et al., 2015), tissue distribution, an individual's underlying health issues, detoxification capacity, and the risk factors associated with NSF (Schlaudecker & Bernheisel, 2009), such as renal impairment or acute kidney injury following GBCA exposure.

The symptoms associated with GDD are listed below and closely mirror those of NSF. An asterisk is next to symptoms ranked in the top 28 of this survey's NSF Group (Table 14). Although head pain and hearing problems did not rank in the top 28 of the NSF group, both appeared in the top 20 of the WITH and WITHOUT Groups (Table 13).

"Subcutaneous tissue loss" was the only GDD symptom not listed in our survey, but involvement of subcutaneous tissue is reported in NSF literature (Zou et al., 2011; Shabana et al., 2012), indicating that it is not unique to GDD.

Some terminological differences exist between the GDD literature and our dataset, though they describe equivalent clinical features (for example, Imbalance = Balance Issues; Pins and Needles sensation = Tingling/Prickling sensations; Hearing problems = Tinnitus) (See Tables 12 and 13).

For reference, we include the symptoms of GDD as listed in, *Gadolinium Deposition Disease – Current State of Knowledge and Expert Opinion (2023)*. (Symptoms with an asterisk are ranked in the top 28 of this survey's NSF Group).

Gadolinium Deposition Disease (GDD) Symptoms:

*Fatigue
*Imbalance
*Pins and needles sensation (often hands)
*Cognitive impairment, including brain fog & memory loss
*Skin crawling
*Skin morphology changes, including progressive thickening and discoloration
Subcutaneous tissue loss (classic face and hands)
Head pain
*Bone pain (rib pain classical)
*Joint pain (commonly large joints like knee & hip)
*Muscle fasciculation
*Vision problems including blurred vision & dry eyes
*Burning sensation skin and/or deep tissue
Hearing problems
*Gastrointestinal issues (vomiting, diarrhea, hypotonia)
*Cardiac arrhythmias

Overall, the overlap in symptom profiles points to a single gadolinium-induced disease process expressed with varying intensity. Depending on exposure, tissue burden, and individual susceptibility, this process may manifest as subtle neurological or musculoskeletal symptoms or progress to the systemic fibrosis seen in NSF. Viewing these conditions as a continuum unifies disparate observations and provides a clearer basis for understanding and managing gadolinium-related disease

Undiagnosed NSF

Identifying patients with NSF remains challenging, as we were only able to find 8 cases for the NSF Group, and 7 are from the United States. Reports from European participants and clinicians indicated that there are currently no recognized physicians or

hospitals specializing in the diagnosis or management of 'NSF' in many European countries. However, that problem is not unique to Europe and has also been reported in the U.S. and elsewhere.

Patients frequently report difficulty obtaining an accurate diagnosis, as well as follow-up care. Such diagnostic gaps are concerning, as they likely contribute to missed or delayed recognition of NSF, which may obscure the true frequency of Gd-related adverse outcomes following GBCA administration.

The absence of standardized diagnostic criteria for NSF and the recognition that a similar disease process may occur in patients with normal renal function likely contributes to persistent underdiagnosis worldwide. These observations highlight the important need for increased clinician awareness and the development of clear diagnostic and management frameworks.

Gd-induced Systemic Fibrosis

In 2009, Marckmann wrote, "It may be time to consider renaming NSF to what it really seems to be, which is Gd-induced systemic fibrosis." Likewise, Wagner (2016) and Kay (2008) argued that the term "nephrogenic systemic fibrosis" should be changed to reflect that gadolinium can induce systemic fibrosis even in the absence of severe renal impairment. While our survey cannot determine whether retained gadolinium causes fibrosis in all patients, the accumulating evidence suggests that the current terminology may not adequately reflect the broader range of gadolinium-associated findings now being reported. Whatever the nomenclature, it should allow for inclusion of patients with normal renal function and recognize that symptom severity may vary, as was also observed among patients with NSF.

Before the FDA's 2015 communication recognizing gadolinium retention in patients with normal renal function, susceptibility to gadolinium-related injury was believed to be limited to those with renal impairment. However, based on what we know now, perhaps the risk exists with varying degrees of severity for all patients exposed to GBCAs.

Long-Term Patient-Centered Outcomes: A Critical Gap in GBCA Research

A significant concern in the evaluation of GBCA safety is the historical inadequacy of research in assessing long-term, patient-centered outcomes. The initial clinical trials supporting the approval of first-generation GBCAs in the 1980's and early 1990's, such as gadopentetate dimeglumine (Magnevist®), primarily focused on acute safety and short-term events.

This narrow evidentiary pattern continues into recent decades, as shown in a 2024 paper on gadobutrol (Gadovist®) reviewing 45 clinical studies in the last 25 years (Endrikat et al., 2024). It also focuses on the short-term, immediate effects of the contrast agent, acknowledging that long-term data on tissue Gd presence and clinical effects are still absent, with no availability of prospective and controlled long-term data. Despite this data gap, the authors of that paper arrived at the same conclusion frequently drawn in the GBCA literature, stating that no causal relationship has been confirmed between GBCA exposure and the chronic symptom clusters reported by patients with normal renal function.

To date, there are no randomized clinical trials that have robustly excluded long-term clinical effects of gadolinium retention. Given the objective evidence of tissue retention (e.g., bone and brain) in humans and animals (Darrah et al., 2009; Murata et al., 2016; Kobayashi et al., 2021), translational animal and neuropathic findings (Radbruch et al., 2020; Krämer et al., 2023), and consistent patient-reported multisystem symptom clusters (Burke et al., 2016; current survey), the accumulating body of evidence constitutes a notable safety signal that justifies prospective, controlled clinical research.

The findings from this Patient Survey provide novel data on the potential long-term adverse effects of gadolinium retention in all patient populations, underscoring the need for systematic investigation by unbiased, independent researchers. Adverse events related to GBCAs go undetected due to the underreporting to the FDA and other regulatory bodies.

It is important that clinicians and patients report serious adverse events after MRIs with a GBCA to the FDA or appropriate governing authority. In the U.S., it can be done online via MedWatch: www.accessdata.fda.gov/scripts/medwatch/
In Europe (EMA EudraVigilance): https://www.adrreports.eu/en/

Retrospective Research

We can assist with finding study subjects for retrospective research studies to determine how Gd may be affecting patients with normal renal function, including those who received only one GBCA and have confirmation of long-term Gd retention.

CONCLUSION

The assertion that gadolinium-based contrast agents (GBCAs) have a long history of safety conflates prolonged use with evidence of patient-centered safety. The historical record demonstrates delayed recognition of severe harm, such as nephrogenic systemic fibrosis (NSF), official acknowledgment of long-term tissue retention of gadolinium including in patients with normal renal function, regulatory restrictions and warnings, and widespread under-documentation of imaging correlates.

Mechanistic data support biologic plausibility for chronic neurologic and systemic effects from retained gadolinium, yet robust data on mortality, disability, quality of life, and work capacity remain scarce. In this context, the precautionary principle and transparent consent are warranted.

From the results of this Patient Survey, we believe the following conclusions can be reached:

- The symptoms reported by those with normal renal function closely match the early phase symptoms of NSF as well as the responses of the NSF Group in this survey. While many may be milder in intensity than full-blown NSF, this pattern consistency supports the hypothesis of a gadolinium-related symptom spectrum that extends to those with normal renal function and warrants prospective investigation.

- Patients with normal renal function report symptoms ranging from mild to life-altering. Absence of systematic symptom documentation in peer-reviewed literature has contributed to clinical underrecognition and diagnostic uncertainty, which patient advocates identify as compounding patient distress and delaying appropriate evaluation.

- Evidence of harm can be found in how body systems *dysfunction* due to gadolinium's interference with various processes, particularly those that require calcium for proper function. The number of survey responses linked to the nervous system is consistent with gadolinium's documented toxic effects on calcium channels.

- Because gadolinium is released slowly from bone over an undetermined duration, individuals who are initially asymptomatic could potentially develop symptoms associated with gadolinium retention later.

- In Unconfounded Cases, in which gadolinium retention and GBCA exposure to either a linear or a macrocyclic GBCA (Table 16) were confirmed, the consistent symptoms observed across both groups indicate that the associations are not confined to a single GBCA class.

- The Patient Survey results warrant a comprehensive investigation into the long-term adverse health effects of gadolinium retained in connective tissues and glandular tissues in all patient populations.

- The symptoms data from this Patient Survey combined with the FDA's 2007 Memorandum that stated, "*unchelated gadolinium is a very toxic compound, particularly to the liver and to calcium channels*," warrant acknowledgement that retained gadolinium can cause harm to patients with normal renal function, just as it did to some renally impaired patients diagnosed with NSF.

We do not know why some patients with normal renal function who received a GBCA report persistent symptoms after their MRIs while others do not. However, a similar situation occurred with NSF, when not all patients with end-stage renal disease who were administered a linear GBCA developed NSF-like symptoms. While the explanation remains unknown, the finding nevertheless occurred, and it was recognized by the FDA and other governing authorities worldwide.

We believe a similar recognition for patients with normal renal function is long overdue.

In summary, the symptom profile reported by gadolinium-exposed patients without renal impairment closely parallels that described in early-phase NSF. This pattern is reproduced among survey participants with clearly defined single-agent exposures and laboratory evidence of gadolinium retention. Collectively, these findings support recognition of a consistent NSF-like symptom signature associated with gadolinium exposure in all patient populations and warrant further investigation.

Note: Patient Survey results pertaining to objective medical signs of abnormalities after contrast administration will be released in a separate paper: *Report 2: Signs of Systemic Abnormalities*.

Other Reports by The Lighthouse Project

On page 38, Section 2.4.4.6, of the Briefing Document for the September 8, 2017, Medical Imaging Drugs Advisory Committee Meeting about gadolinium retention in patients with normal renal function, reports produced by The Lighthouse Project about symptoms and gadolinium urine levels were referenced (Williams & Grimm, 2014; Grimm & Williams, 2017). The FDA noted that the data collection was conducted by a support group of patients with self-reported gadolinium toxicity. It

concluded by saying, "*Those reports have been generated by the Lighthouse Project and should be acknowledged even though they have not been published in peer-reviewed journals*" (See Appendix 5). In collaboration with authors Sarah Ratnam and Catriona Walsh, the report of this Patient Survey was produced with the same high standards applied to those earlier reports; the important data contained herein should also be acknowledged and given appropriate attention.

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Financial Interests: Author, Catriona Walsh, is the founder of The Food Phoenix and author of *Contrasts: More than Meets the MRI*. No other authors have financial interests to declare.

Non-Financial & Personal Interests: All authors of this report have been personally affected by adverse events following the administration of gadolinium-based contrast agents. The coauthors are unpaid patient advocates who volunteer their time to support and advocate for patients by raising awareness and recognition of the potential long-term adverse effects of retained gadolinium in all patient populations.

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Appendix 1 – Gadolinium-Based Contrast Agent Trademark Information

Gadolinium-based Contrast Agent Product Information as of August 2025			
Brand Name & Manufacturer	**Other Names**	**Molecular Structure**	**FDA Approval**
Ablavar®/Vasovist® Lantheus Medical Imaging, Inc.	Gd-DTPA (gadofosveset trisodium)	Linear, ionic	2008 - Withdrawn from market 2017
Clariscan™ GE Healthcare Inc.	Gd-DOTA (gadoterate meglumine)	Macrocyclic, ionic	2019
Dotarem® Guerbet LLC	Gd-DOTA (gadoterate meglumine)	Macrocyclic, ionic	2013
Elucirem™ Guerbet LLC	(gadopiclenol)	Macrocyclic, non-ionic	2022
Eovist®/Primovist® Bayer HealthCare Pharmaceuticals	Gd-EOB-DTPA (gadoxetate disodium)	Linear, ionic	2008
Gadovist®/Gadavist® Bayer HealthCare Pharmaceuticals	Gd-BT-DO3A (gadobutrol)	Macrocyclic, non-ionic	2011
Gadobutrol Injection Fresenius Kabi USA, LLC.	(gadobutrol)	Macrocyclic, non-ionic	2023/Generic
Gadoterate Meglumine Injection Fresenium Kabi USA, LLC	(gadoterate meglumine)	Macrocyclic, ionic	2022/Generic
Magnevist® Bayer HealthCare Pharmaceuticals	Gd-DTPA (gadopentetate dimeglumine)	Linear, ionic	1988 - Withdrawn from market 2019
MultiHance® Bracco Diagnostics Inc.	Gd-BOPTA (gadobenate dimeglumine)	Linear, ionic	2004
Omniscan™ GE Healthcare Inc.	Gd-DTPA-BMA (gadodiamide)	Linear, non-ionic	1993
OptiMark™ Guerbet LLC	Gd-DTPA-BMEA (gadoversetamide)	Linear, non-ionic	1999 - Discontinued by mfr. in 2018
ProHance® Bracco Diagnostics Inc.	Gd-HP-DO3A (gadoteridol)	Macrocyclic, non-ionic	1992
Vueway® Bracco Diagnostics Inc.	(gadopiclenol)	Macrocyclic, non-ionic	2022

Appendix 2 – New Diagnoses / Autoimmune Diseases or Other Heath Conditions

Patients were asked if they had been diagnosed with an autoimmune disease or other health condition that they believe relates to the signs or symptoms they identified elsewhere in the Patient Survey questionnaire. Unless noted otherwise, there was one case reported for each of the diagnoses or diseases listed.

NEW DIAGNOSES / AUTOIMMUNE DISEASES OR OTHER HEALTH CONDITIONS		
WITH Results Group	**WITH Results Group**	**WITHOUT Results Group**
Multiple Sclerosis (after MRIs – 2 cases)	Small Fiber Neuropathy (SFN) (6 cases)	Myasthenia Gravis
Dementia	Neuropathy (3 cases)	Stroke
Cognitive deficits (3 cases)	Vascular neuropathy	Functional Cognitive Disorder
Encephalomalacia	Motor neuron disease (MND)	Functional Neurological Disorder
Brain lesions	Somatic dysfunction	High cerebrospinal fluid pressure
Systemic Lupus Erythematosus (4)	Autonomic dysfunction	Systemic Lupus Erythematous (SLE)
Antiphospholipid syndrome (APS)	Thrombotic vasculitis	Raynaud's disease (3 cases)
Anxiety & depression	Behcet's vasculitis	Anxiety
Diabetes	Myopathy	Diabetes (2 cases)
Iron deficiency anemia	Myelopathy	Autoimmune hemolytic anemia (AIHA)
Celiac disease	Benign fasciculation syndrome	Celiac disease
Crohn's disease	Chemical-induced Asthma	Scleroderma
Gut dysbiosis	Multiple Chemical Sensitivity (2 cases)	Nephrotic syndrome
Bowel blockage	Allodynia	New onset chronic kidney disease
Hashimoto's thyroiditis (4 cases)	Hearing loss	Vasovagal syncope
Hypothyroidism (3 cases)	TMJ	Hashimoto's thyroiditis (3 cases)
Addison's disease	Eosinophilic esophagitis (EoE)	Optic migraines
Sjogren's syndrome (4 cases)	Orofacial granulomatosis	Sjogren's syndrome (2 cases)
Immune deficiency disorder	Wegener's granulomatosis	Fibromyalgia (6 cases)
Fibromyalgia (7 cases)	Idiopathic pruritus	Mast Cell Activation Syndrome (2 cases)
Mast Cell Activation Syndrome (5 cases)	Psoriatic arthritis	Thoracic Outlet Syndrome (TOS)
Chronic fatigue syndrome (CFS)	Rheumatoid arthritis (RA)	Chronic fatigue syndrome (CFS)
Adrenal fatigue (2 cases)	Thoracic calcification	Vitiligo
NAFLD - Fatty liver (3 cases)	Cervical, thoracic & lumbar spine disease (onset after 1 MRI with GBCA)	Chronic Inflammatory Demyelinating Polyneuropathy (CIPD)
Autoimmune liver disease / fibrosis and atrophy of liver	Gadolinium Deposition Disease (2 cases)	Postural orthostatic tachycardia syndrome (POTS) (2 cases)
Postural orthostatic tachycardia syndrome (POTS)	MGUS - Monoclonal Gammopathy of Unknown Significance (2 cases)	Ankylosing spondylitis Morphea
Autoimmune Autonomic Ganglionopathy		Sarcoidosis Connective tissue disease
Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (4 cases)		Idiopathic autoimmune disease Immunoglobulin deficiency
Autoimmune Lymphoproliferative Syndrome Type 1 (ALP3)		Psoriatic arthritis
		NSF GROUP - NEW DIAGNOSIS
		Diabetes
		Sjorgen's syndrome
		Unspecified autoimmune disease

Appendix 3 – Symptoms That Have Worsened or Continued

Unless noted otherwise, there was one case reported for each symptom listed.

SYMPTOMS THAT HAVE WORSENED OR CONTINUED	
WITH Results Group	**WITHOUT Results Group**
Widespread generalize pain (5 cases)	Pain in injected arm (right arm)
Joint pain (7 cases)	Joint pain (3 cases)
Rib pain (2 cases)	Bone pain
Bone pain (4 cases)	Back pain (2 cases)
Back pain (3 cases)	Legs & knees cannot bend
Painful hands	Neuropathy (2 cases)
Severe osteoporosis	Stabbing pain
Neuromuscular pain	Muscle wasting
Neuropathy (9 cases)	Muscle weakness
Neurological symptoms	Continued weakening of facial muscles
Balance issues	Dystonia
Vertigo/dizziness (2 cases)	Dizziness
Nonstop itching & burning all over body	Arthritis worse
Fasciculations/muscle twitching (5 cases)	Connective tissue disease worse
Tremors	Autoimmune issues
Muscle cramps (2 cases)	Nephrotic syndrome
Muscle pain	Pain in bladder
Stiff muscles	Reduced kidney function
Muscle wasting	Sjogren's-like symptoms
Muscle weakness	Fatigue
Loss of movement	Tinnitus
Recurring sprains & tendon/ligament issues	Ongoing vascular issues
Can't wear closed shoes due to numbness & pain	Memory loss 48hrs after MRI has worsened to the point of needing constant daily care.
Memory issues (3 cases)	Cognitive issues (4 cases)
Brain function (3 cases)	Difficulty with speech
Vision/Eye issues (5 cases)	Confusion
Visual disturbances	Depression
Fatigue (5 cases)	Vision/Eye issues
Tinnitus (5 cases)	Mast Cell Activation Syndrome
Skin lipomas/larger & spread to more areas	Restlessness
Skin thickening	Hair loss
Changes to skin (4 cases)	Extensive vitiligo
Thickened tissue	Heart palpitations
Scalp lesion (not psoriasis)	GI issues (3 cases)
Hair loss/thinning	Numerous skin changes
Shortness of breath/lung issues (4 cases)	Receding gums
Difficulty swallowing	Difficulty sleeping due to pain
GI issues	Food sensitivity
Labile hypertension	
Palpitations (2 cases)	**NSF GROUP – WORSE or CONTINUED**
Irregular heartbeat	AFib is moderate & treated with meds
Can't regulate body temperature	Lungs abnormal findings on scan
Allergic reactions more frequent & severe	Lymphedema is worse
Sensory sensitivity	Organ fibrosis is worse
Food & Heat sensitivity	Contractures are better
Now depend on others with daily living	Skin better in terms of thickening appearance

Appendix 4 – May 15, 2007, FDA Memorandum to the File about GBCAs & NSF

Blue box was added by authors to highlight relevant text in the document.

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

MEMORANDUM TO THE FILE

i. **NDA: 20-123, 22-066** **Product:** Omniscan
ii. **NDA**: **19-596, 21-037** **Product**: Magnevist
iii. **NDA: 20-976, 20-937,20-975** **Product**: OptiMARK
iv. **NDA**: **21-357, 21-358** **Product:** MultiHance
v. **NDA** : 20-131, 21-489 **Product:** ProHance

Topic: Gadolinium-Based Contrast Agents (GBCAs) and Nephrogenic Systemic Fibrosis (NSF) Date Completed: 5/15/07

Medical Reviewer: Melanie Blank, MD

I. OBJECTIVE

The purpose of this memorandum is to summarize the evidence for the causative role of gadolinium-based contrast agents in the development of NSF and to describe the risk modification steps culminating with the proposal to request revised class labeling from the drug manufacturers that includes a warning.

II. SUMMARY

a. GBCAs are gadolinium chelates (large organic molecules with a total of 8 bonds, 7 to Gd+++ (gadolinium) and 1 to H_2O). This structure makes the Gadolinium paramagnetic so that it can move with higher relaxivity in a strong magnetic field and therefore appear differently on an MRI (Magnetic Resonance Imaging) or MRA (Magnetic Resonance Angiography) scan than the surrounding tissue.

b. Unchelated gadolinium is a very toxic compound, particularly to the liver and to calcium channels

c. 5 gadolinium contrast agents are FDA approved for MRI. No GBCAs are FDA approved for MRA

d. GBCAs are administered IV and are indicated for CNS and body/liver MRI

i. Omniscan: CNS and total body
ii. Magnevist: CNS and total body
iii. OptiMARK: CNS and liver
iv. MultiHance: CNS
v. ProHance: CNS and head/neck

e. GBCAs are renally excreted and therefore severe renal insufficiency prolongs exposure

f. GBCAs are eliminated by hemodialysis but clearly not as efficiently as the normal kidney

g. Peritoneal dialysis is not as efficient as hemodialysis in clearing GBCAs.

Appendix 5, page 1 of 3 – FDA 2017 Briefing Document, September 8, 2017

Medical Imaging Drugs Advisory Committee Meeting

Gadolinium Retention after Gadolinium Based Contrast Magnetic Resonance Imaging in Patients with Normal Renal Function

Briefing Document
September 8, 2017

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this safety issue to the advisory committee in order to gain the committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

1

Appendix 5, page 2 of 3 – FDA 2017 Briefing Document (page 38)

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deep grey nuclei, but also hemispheric white matter and cerebellar cortex in adults and children, the majority of which had normal renal function, corroborating imaging study findings.[6,107-112] Post-mortem gadolinium retention in brain tissue has been reported for linear GBCAs, but also in seven patients who have exclusively received macrocyclic GBCAs.[109] Higher post-mortem concentrations have been generally reported in the dentate nucleus and globus pallidus compared to other brain regions. At an ultrastructural level, gadolinium retention has been localized to capillary endothelium and neural tissue (interstitium and nuclei) in three studies.[6,111,112] While three studies did not identify any gross histopathologic changes on light microscopy using hematoxylin-eosin stain,[6,109,112,113] one small case series in pediatric patients revealed histopathological changes using neurofilament immunohistochemistry in two out of three patients with findings consisting of mild to severe gliosis of the dentate nucleus with prominent axonal spheroids.[111]

One study found a positive correlation between gadolinium retention in neural tissue and T1-weighted signal intensity on MRI without contrast.[6] None of the cases in those post-mortem studies had any pre-mortem adverse events reported, although no studies explicitly stated whether pre-mortem adverse events were sought beyond clinical information such as immediate cause of death, imaging indication or major diagnosis, and laboratory results. A summary of those post-mortem studies is presented in Appendix K. Gadolinium retention was also observed in primary brain tumor specimens after GBCA administration, especially with less stable linear non-ionic GBCAs (gadodiamide) compared to more stable linear ionic GBCAs (gadobenic acid), with an interval between the first administration and the specimen collection ranging from 0 to 2556 days.[114]

Systemic retention in a number of tissues including skin, bone, and liver has been reported in patients with normal renal function and the retention in bone reportedly occurred at much higher level than in the brain.[109,113,115-119] Those publications did not describe symptoms attributable to retention in those tissues although they were not designed to collect such information. . Extracranial sites have been suggested as surrogates for brain tissue given the limitations inherent to MRI-based gadolinium measurement in brain tissue.[120] Zinc exposure and siderosis have been suggested as possible risk factors for systemic gadolinium retention.[118,121] In addition, brain irradiation and progressive forms of multiple sclerosis have been associated with T1-weighted hyperintense signal abnormality of the dentate nucleus, but the contribution of prior GBCA administration was not assessed in those studies as they predated the awareness of gadolinium retention.[122,123]

2.4.4.6 Unpublished Reports

A few data collection reports including symptoms and body fluid gadolinium measurements have been conducted by a support group of patients with self-reported gadolinium toxicity. Those reports have been generated by the Lighthouse Project and should be acknowledged even though they have not been published in peer-reviewed journals.[124,125]

2.5 Discussion

The primary purpose of this review was to identify adverse events in conjunction with gadolinium retention after exposure to GBCAs in patients with normal renal function reported to the FAERS database and in the medical literature. We considered cases that reported detectable

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