Background on Risk Factors

To better understand what has been published about the risk factors related to Gadolinium retention, you have to remember that much of the research has been focused on trying to determine why patients with severe renal impairment developed Nephrogenic Systemic Fibrosis (NSF) after having MRIs with a Gadolinium-Based Contrast Agent (GBCA). While some risk factors are specific to those with renal impairment or liver failure, many risk factors could apply to all GBCA-exposed patients. Our focus will be on those risk factors for Gadolinium retention that have the potential to affect all patients.

Note that the long-term effects of retained Gadolinium are still unknown and cumulative dosage is considered by some researchers to pose a long-term risk to potentially everyone at some point in the future, including patients with normal renal (kidney) function.[1,2,3,4,5,6]

1% Retention Factor

It appears that just having an MRI or MRA with contrast may put everyone at risk of retaining at least some of the toxic Gadolinium ion. It has been estimated that approximately 1% or 15 mg of the 1.5 grams of Gadolinium (Gd) contained in each standard dose of contrast (0.1 mmol/kg body weight) may be retained in the body where it will be deposited primarily in bone.[7,8] A 2004 study by Gibby et al found that Gadolinium was deposited in bone tissue removed from patients with normal renal function within four days of GBCA administration.[9] A 2009 study by Darrah et al confirmed incorporation of Gadolinium into bone where it was retained for longer than 8-years after GBCA exposure.[10]

Impaired Renal Function

The primary risk factor for Gadolinium retention is having severely impaired renal function, meaning having an estimated glomerular filtration rate (eGFR) below 30.[11] Since GBCAs are cleared from the body primarily via the kidneys, poor kidney function causes the GBCA to remain in the body for a much longer period of time. That increases the risk of the Gadolinium ion and ligand separating which results in large quantities of toxic Gadolinium being retained in the body. [12] The end result can be NSF.

Stability of the Agent, Cumulative Dosage and High Dosage

Besides impaired renal function, the stability of the contrast agent that is administered as well as cumulative dosage and high dosage also contribute to retention of Gadolinium from the GBCA.[9,13] The linear GBCAs Omniscan, Optimark and Magnevist are considered to be the least stable; however, there are cases of NSF linked to macrocyclic agents as well. (See Background on GBCAs for details.)

While the literature says these are contributing factors for NSF in the renally-impaired, the urine test results presented in our Self-Study of Retained Gadolinium and Appendix 1 of our Symptom Survey Report indicate that they may also cause Gadolinium retention in patients with normal renal function (meaning eGFR >60). Although our papers have not been published in medical journals, they are factual and supported by findings in the published, peer-reviewed literature.

Altered Blood-Brain Barrier

Another risk factor for Gadolinium retention that seems to be somewhat overlooked is having a compromised blood-brain barrier (BBB). The presence of a tumor or lesion, or anything that alters the blood-brain barrier can result in Gadolinium being deposited in brain tissue regardless of the patient's level of renal function. GBCA product labeling indicates that Gadolinium-Based Contrast Agents "do not cross an intact blood-brain barrier"; however, "disruption of the blood-brain barrier" or "abnormal vascularity" allows accumulation in lesions such as neoplasms (tumors), abscesses, and subacute infarcts.[14,15,16,17,18,19,20,21,22]

There is growing evidence of deposited Gadolinium remaining in brain tissue.[23,24,25] Two recent studies involving patients with Multiple Sclerosis (MS) or brain metastases reported increasing signal intensity on unenhanced T1-weighted MR images of the brain within the Dentate Nucleus after multiple contrast-enhanced MRIs – including in patients with normal renal function.[26,27]

Besides the presence of a tumor or lesion, there appear to be many other ways that the blood-brain barrier might be crossed or temporarily altered. Whenever that occurs, the risk of Gadolinium being retained in brain tissue may be increased. See Background on Gadolinium for more details about blood-brain barrier disruption.

Transmetallation

Other than renal impairment, researchers have said that transmetallation presents the greatest potential risk for the release of the toxic metal ion from the chelate.[28,29] Transmetallation is the displacement of the Gadolinium ion (Gd^{3+}) from the chelate (ligand) by other metal ions in the body such as zinc, calcium, copper and iron.[5] The metals can work at the same time to destabilize the GBCA complex which can result in Gadolinium remaining in the body.

Since at least 1992, dechelation or separation of the ion and ligand due to transmetallation and acid dissociation was confirmed in animal studies.[30,31,32] Transmetallation can and has occurred in people with normal renal function.[33,34,35]

The risk of transmetallation appears to be greater with the nonionic, linear GBCAs – Omniscan and Optimark.[36,37] However, all linear GBCAs are considered to be less stable than the macrocyclic agents.[38,39,40] (See Background on GBCAs for more details.)

Extravasation

Extravasation occurs during the intravenous injection of the Gadolinium-Based Contrast Agent. The administered GBCA is accidentally injected into the surrounding soft tissue instead of directly into the vein. Extravasation can cause edema, inflammation, and necrosis of the tissue.[12,41] Besides damaging the tissue, that portion of the GBCA dosage that was directly deposited in tissue could result in Gadolinium retention.

Acute Kidney Injury (AKI)

An Acute Kidney Injury or AKI is a common clinical problem and often occurs in the elderly, and during hospitalizations and after surgeries.[42] GBCAs were thought to be safer to use in the renally-impaired; however, that has not proven to be the case. Gadolinium-based Contrast Agents were found to be more nephrotoxic than iodinated contrast media in equivalent X-ray attenuating doses.[43,44]

Some of the causes of AKI include the use of radiocontrast dyes, diuretics, NSAIDs, ACE Inhibitors, Angiotensin II Receptor Blockers, Statins, Fluoroquinolones, and Tetracyclines.[45]

There are conflicting reports regarding the nephrotoxic effects of GBCAs.[46] However, in 2006, Akgun et al reported the first renal biopsy of a patient with acute renal failure associated with a GBCA to emphasize their potential nephrotoxicity.[47] Note that acute renal failure (ARF) is now known as acute kidney injury (AKI).

Acidosis

Acidosis is a condition in which the body has more acid than normal. This can cause the pH of the blood and body tissues to fall below the healthy range of 7.35-7.45. Some of the causes of acidosis include: high protein diets, excess coffee and alcohol consumption, chronic disease, toxic exposure, certain medications, prolonged vigorous exercise, diabetes, cancer, dehydration, low blood sugar, poor digestion, the normal process of aging, liver failure, and kidney disease.[48] It is well established that the rate of Gadolinium release increases with decreasing pH.[49]

Proinflammatory Event

The occurrence of a proinflammatory event near the time of your contrast-enhanced MRI or MRA can increase your risk of retaining Gadolinium from the administered GBCA. Proinflammatory events include recent surgery, infection, vascular procedures or thrombosis.[50]

The Bottom Line

As you can see, there are many factors that could result in a patient retaining varying amounts of Gadolinium from the Gadolinium-Based Contrast Agent regardless of his or her level of renal function. What is not clear is why some patients become symptomatic while others do not. It remains to be seen if those patients will become symptomatic at some later point in time or after additional doses of contrast. It is possible that some patients attribute their symptoms to whatever condition caused them to have a contrast-enhanced MRI or MRA.

If you have unexplained symptoms that you believe were caused by retained Gadolinium from a contrast MRI or MRA, please report it to the FDA by filing a MedWatch Adverse Event Report. Call 1-800-FDA-1088 or report via the FDA website at http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

When filing a report online, remember that Gadolinium-Based Contrast Agents are considered prescription medications or drugs.

Patients outside the U.S. should report to their country's equivalent governing agency.

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