Nephrogenic Systemic Fibrosis: A Radiologic Perspective

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THE PROBLEM

The first case of what ultimately would be called Nephrogenic Systemic Fibrosis (NSF) was recognized in 1997 and subsequently reported in 2000.[1] Over the ensuing years a growing body of literature has elucidated the clinical picture of the disease and the extent of organ involvement. Although the exact etiology remains unknown, all NSF patients have significant chronic renal impairment (stage 4 or 5) or acute renal failure. In 2006 an association was reported between intravenous gadolinium-based contrast material used for magnetic resonance (MR) imaging and subsequent development of NSF in a small group of dialysis patients in Austria, followed by a larger study from Denmark with similar findings.[2,3] Since then, researchers and government regulators alike have had these contrast agents in their crosshairs.

Over 200 million patients have received gadolinium-based contrast agents since the 1980s. Gadolinium (Gd^{3+}; atomic number sixty-four) shortens T1 relaxation* of tissues, which brightens many abnormalities on MR scans, compared with background tissues.[4] This phenomenon allows easier detection of lesions and evaluation of abnormalities of flow and perfusion.[5] These contrast agents all use gadolinium bound to a ligand, which forms an organically stable chelate. It is important that the chelate not release free gadolinium (Gd^{3+}), which is highly toxic, in part because it is similar to Ca^{2+} in size and charge. When free gadolinium replaces calcium in biochemical pathways, many physiological processes which depend on Ca^{2+} are inhibited or depressed,[6] including muscle contraction (smooth, skeletal, and heart), certain enzyme reactions, and some liver functions.

*This is a measure of the time to "relaxation," (return to an equilibrium energy state) of protons (hydrogen ions) which have been temporarily excited by radiofrequency energy applied by coils placed close to the tissues of interest. The measurement of this phenomenon depends upon the presence of a surrounding magnetic field created by the MR imaging machine.

Since the first publication of a possible association between gadolinium and NSF, deposits of gadolinium have been found in tissue samples from the woody indurated skin lesions of patients with NSF,[7,8] which implies in vivo uncoupling of gadolinium from it's ligand. A more detailed description of these compounds is therefore necessary:

Table 1 lists the currently approved gadolinium based contrast agents in use throughout the world. All of these agents fall into one of two structurally distinct categories: cyclic or linear chelates.[6] Cyclic chelates morphologically form a cavity that in effect surrounds Gd^{3+} in a cage, whereas linear chelates have a more open configuration. The other important property of these molecules is their charge, since ionic chelates are less likely than nonionic chelates to release free Gad^{3+}. When the properties of structure *and* charge are considered together, the evidence indicates that non-ionic *linear* chelates are most likely to release free Gd^{3+} ; ionic *cyclic* chelates are least likely to do so;[6,9,10] while ionic *linear* chelates and non-ionic *cyclic* chelates probably fall between these two ends of the spectrum.

Initial case reports of NSF submittted to the FDA and its British counterpart overwhelmingly implicated Omniscan as the causative MR contrast agent when used in patients with renal impairment. There were additional reports of renal dialysis patients who received OptiMARK prior to development of NSF. Both contrast agents are non-ionic cyclic gadolinium chelates. Since then, additional cases of NSF have been reported, including at least 78 cases following Magnevist and 1 in a patient who received both Omniscan and MultiHance. To date over 250 cases have been reported, of which 180 involved Omniscan.[11]

The US and British regulatory agencies have taken different approaches to the accumulating data. The FDA does not differentiate between any of the five US-approved gadolinium based contrast agents;[12] it

TABLE 1 : CURRENTLY MARKETED GADOLINIUM CONTRAST AGENTS.*

Brand name	Generic name	Acronym	Chemical structure	Charge	Cases of NSF
Omniscan	gadodiamide	Gd-DTPA-BMA	Linear	Non-ionic	Yes
OptiMARK	gadoversetamide	Gd-DTPA-BMEA	Linear	Non-ionic	Yes
Magnevist	gadopentetate dimeglumine	Gd-DTPA	Linear	Ionic	Yes
MultiHance	gadobenate dimeglumine	Gd-BOPTA	Linear	Ionic	Yes
Primovist**	gadoxetic acid disodium salt	Gd-EOB-DTPA	Linear	Ionic	No
Vasovist**	gadofosveset trisodium	Gd-DTPA	Linear	Ionic	No
ProHance	gadoteridol	Gd-HP-DO3A	Cyclic	Non-ionic	No
Gadovist**	gadobutrol	Gd-BT-DO3A	Cyclic	Non-ionic	No
Dotarem**	gadoterate meglumine	Gd-DOTA	Cyclic	Ionic	No

*Modified from Public Assessment Report UK Commission of Human Medicine p. 10.
**Primovist, Vasovist, Gadovist, and Dotarem are not licensed in USA.

recommends that physicians weigh the risks and benefits of gadolinium-based contrast agents in patients with severe renal insufficiency (GFR of < 30 mL/min/1.73 m^2), and use alternative imaging methods when possible. The FDA'a British counterpart, the MHRA (Medical Healthcare products Regulatory Agency) feels that the gadolinium-based contrast agents do not all pose the same risks because of their distinct physiochemical properties.[11] The MHRA advises a step-wise approach, and recommends that Omniscan, OptiMARK, and Magnevist should not be used in at risk patients outlined above.

THE SOLUTION

What is a radiologist to do? More than 21 million gadolinium injected MR scans were performed in 2006,[13] and approximately 250 cases of gadolinium-associated NSF have been reported in registries to date. The key to navigating through this information is to identify the population at risk,[14] patients with stage 4 chronic kidney disease (an estimated GFR of <30 mL/min/1.73 m^2), stage 5 chronic kidney (estimated GFR of <15 mL/min/1.73 m^2), or acute renal failure. Within this group the registries suggest that the ESRD dialysis patient may be the most at risk with an estimated 2.4% incidence of NSF after an injection of a gadolinium chelate.[15]

At Lancaster General Hospital we focus on the at-risk population and do the following:

All inpatients and any outpatients with a history of renal disease must have a serum creatine and estimated GFR measured prior to gadolinium injection.

At-risk patients (as defined above) undergo further review by the supervising radiologist to determine possible alternative imaging studies or to confirm the necessity of an MR study with gadolinium contrast.

All at-risk patients approved for gadolinium injection are asked for informed consent, and are then injected with MultiHance rather than Magnevist (which was used exclusively in the past).

Dialysis patients who receive gadolinium injections receive dialysis promptly following the MR examination.

CONCLUSIONS

NSF remains an incompletely understood rare disease. Recent evidence has implicated a possible link with the injection of certain gadolinium-based chelates. Free Gd^{3+} appears to be part of a multifactorial process that leads to debilitating and potentially fatal systemic fibrosis in a small group of patients. The evolving understanding of this disease will continue to challenge the radiology community to define the patient at risk and to find alternative imaging solutions.

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