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Nephrogenic system fibrosis: A radiologist's practical perspective

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Abstract

This manuscript will provide the background current understanding of Nephrogenic Systemic Fibrosis (NSF) necessary to be appreciated by radiologists who are practicing cross-sectional imaging including gadolinium based contrast agent (Gd-CA) enhanced MRI. Examination of the known risk factors for NSF provides a practical list of considerations including an appreciation of the degree of patient renal function, or dysfunction, and the type and dose of Gd-CA used. Data is presented to argue that we must consider not only the one-time dose, but particularly the cumulative Gd-CA life-time dose administered to a patient. Using the foundation of known risk factors for NSF, we can then assemble a working list of strategies that can be utilized in an imaging practice to minimize the risk of NSF for all patients, including those at highest risk for this disorder. This list includes a discussion of high stability Gd-CAs, cumulative dose monitoring and limits, dialysis, and more specific documentation in the medical records. Finally, the issues required to understand the information that should be provided to the patient prior to obtaining informed consent are discussed. The objectives of an informed consent is to ensure that the patient is properly informed and involved in the decision to proceed with a contrast enhanced MRI, and to provide documentation to establish that the medical facilities and the radiologist are themselves well-versed in the risks and benefits when making the decision to use contrast enhanced MRI for particular patients. The process of informed consent requires that there be a consideration of the risks of not performing the contrast enhanced MRI, or the relative risk of performing another test, particularly a contrast enhanced CT. This requires an appreciation of the risks of CT-related ionizing radiation and cancer, and the risk of iodine based contrast agents (I-CA) and contrast induced nephropathy (CIN). Data is presented to show that many, and perhaps the vast majority, of renal dysfunction patients are at greater risk of harm from I-CA related to CT as compared to high stability Gd-CAs used for MRI.

Keywords: Gadolinium; Gadolinium-chelates; Gadolinium based contrast agents; Iodinated contrast; Magnetic resonance imaging; MRI; CT; Nephrogenic systemic fibrosis; NSF; Contrast induced nephropathy; CIN; Kidney; Renal; Dialysis; Informed consent

1. Background

Throughout the history of magnetic resonance imaging (MRI) we have never been faced with so much scrutiny regarding the potential danger in a particular procedure. There is now an intense interest, and in some cases fear, regarding the use of gadolinium based contrast agents (Gd-CAs) for enhanced MRI. Patients, physicians, MR technologists, and administrators have widely become keenly aware of the concerns regarding the association between Gd-CAs and Nephrogenic systemic fibrosis (NSF) in patients with severe renal insufficiency. With the rapid evolution of our appreciation of the relationship between NSF and Gd-CAs, there has also been the potential for a sense of confusion. No doubt that the degree of concern resides partly in the overt pronouncements and warnings from our regulatory bodies, which have themselves been controversial, in the Unites States, the Federal Drug Administration (FDA) issued a non-specific warning against all Gd-CAs neglecting to make any distinction between class of agent [1], and partly from the keen interest from a virtual army of litigators looking to exploit the situation, again a phenomenon particularly descriptive of the situation in the United States. The potential for misconception and uncertainty can be appreciated given that we have only known about NSF since the initial description by Cowper et al. 7 years previously [2], and have only been aware of the potential relationship to Gd-CA administration in patients with severe renal insufficiency less than 2 years previously, since the first reports by Grobner et al. [3] and by Marckmann [4] and Thomsen et al. [5,6].

Here, I will provide a perspective from the view of a practicing radiologist, responsible for the clinical operation of a large

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academic MRI practice within a university hospital setting. The objective is to provide a working model for appreciating what we know of NSF and Gd-CAs, and how to implement a safe and effective set of protocols that can, and should, be implemented in any medical facility performing cross-sectional imaging, including MRI.

One key to effective medical practice as a diagnostic imager derives from understanding the balance between managing an individual patient's risk in having a procedure, versus having a different procedure, or no procedure at all. This entails appreciating the risks, and how to manage those risks. Within this algorithm lies the additional challenge of accepting patterns of diseases and complications of procedures for which the data may rely heavily on inferred observations, as opposed to those outcomes that may be more easily detected and measured. This is particularly a challenge when the event rates are low. Examples would include radiation biology as it pertains to radiation dose levels used in radiology, and, as will be discussed here, as it pertains to NSF in relation to use of certain Gd-CAs and in certain subsets of patients.

2. Highest risk factors

2.1. Renal dysfunction

Almost all documented cases of NSF have occurred in patients with renal dysfunction classified as moderately severe, stage 4 (GFR 15–29 ml/min) or severe, stage 5 (GFR 0–14 ml/min) [7–13]. In the United States most of the NSF cases have occurred in patients on dialysis, although this pattern appears to be somewhat different to that found in European centers for reasons that remain uncertain. In our own center, the pattern clearly demonstrated patients with severe renal dysfunction are at risk [10]: all 9 NSF cases had stage 5 renal disease with all but one patient on dialysis at the time of Gd-CA administration, and this patient started dialysis immediately after the last Gd-CA administration 1 month after a failed renal transplantation. Others have reported cases in acute renal dysfunction [12], where it is more challenging to know exactly what the stage of renal disease is. Furthermore, in patients who are not on dialysis, we must trust that the institution providing the analysis of these patients can determine the renal function of each NSF case at the time of GBCA. While this is straightforward in patients on dialysis, where we know that the patients mostly have minimal GFR well under 15 ml/min, it is not exactly clear how reliably we can trust GFR measurements in other patients. Methods of estimating GFR are particularly inaccurate in cases when the renal function is severely impaired [14]. Furthermore, renal function may vary and unless an accurate GFR measurement is made at the same time that a Gd-CA is administered we can generally only roughly estimate the renal function for any individual under those conditions. Everyone has been relying on retrospective data, mostly acquired prior to our understanding of the relationship of Gd-CA use to NSF. The availability of good documentation is inherently spurious. In any reports where moderate (GFR 30–59 ml/min) renal function is claimed, we must be cautious in the interpretation of these cases. It remains to be shown that any patient with normal renal function has ever developed NSF. Again, observations from our own center argue that a vastly larger number of patients with moderate renal dysfunction have had Gd-CA administrations for MRI studies as compared to dialysis patients, and many more of these patients have had multiple studies with higher cumulative Gd-CA doses, but we have not observed any cases of NSF in this group.

2.2. Type of GBCA

Almost all cases of NSF have been associated with one agent, gadodiamide (Omniscan^{TM}), with the remainder mostly accounted for by gadopentate dimeglumine (Magnevist^{TM}) and gadoversetamide (Optimark^{TM}) [15,16]. The most logical explanation for this pattern is a relation between chelate stability and disease risk. The rationale being that it is the unbound free gadolinium ion that is toxic and is responsible for disease initiation or promotion [17–19]. Omniscan and Optimark are the least thermodynamically stable agents. By distinction, there are yet no fully documented reports in the peer-reviewed literature of other agents causing NSF in humans. Although a few cases have been suspected, these have not yet been fully scrutinized at the time of this writing. More to the point, institutions having NSF cases have accounted for the majority of our understanding of NSF within peer-reviewed publications. Meanwhile, centers without NSF cases have only recently moved towards appropriate documentation and reporting. To date, of over 150 cases in excess of 90% have been associated with Omniscan administrations [5], with the remainder either receiving Optimark, Magnevist, or having a confounding administration history. Other centers, using more stable agents, including macrocyclics, have been indicating that they have been dosing renal failure and dialysis patients similarly to centers with NSF cases, who have used gadodiamide. In addition, we are now seeing another pattern evolve in centers who have previously reported NSF cases using gadodiamide who have since changed to a different more stable GBCA. Dr. Henrik Thomsen of the University of Copenhagen, who has been a leader in helping uncover the relation between Gd-CA stability and NSF and in guiding regulatory policies in Europe, has indicated that their center previously experienced an incidence of 5–6 NSF cases per year, yet has not had a case of NSF since switching from Omniscan to a macrocyclic agent in March 2006, despite continued administrations to renal insufficiency patients [16,20]. In our own center, we have not had another case of NSF since switching to a more stable agent, despite continued administrations to patients with severe renal disease. By the time of this writing, we would have expected to have seen another 3–4 cases based on prior incidence of 2.6% in dialysis patients.

2.3. Dose-effect of Gd-CA

We have clearly seen a pattern that there are differences in the ability of different Gd-CA formulations to induce NSF, and that agent stability may account for these differences; we then have a rationalization to account for why almost all NSF cases have been related to Omniscan. We then must consider dose-effect

relationships. In our study cohort [10] 3 of 9 NSF patients had received only a single dose (0.1 mmol/kg) of Omniscan between 4 and 8 weeks prior to diagnosis of NSF. However, on average, the NSF patients had received 3 doses of Omniscan, with a range of between 1 and 8 doses. Of particular note all but 1 patient had been given only a single dose of Omniscan prior to the clinical onset of NSF. This pattern is similar to the findings at other institutions [21] and strongly supports the following: (1) although a single dose of Omniscan can induce NSF, the NSF incidence rate increases with increasing dose of this agent; (2) cumulative dose over at least weeks, and perhaps years, must be considered an additive risk factor.

2.4. Uncertainties

Extrapolation from the observation that cumulative doses of at least Omniscan result in increasing the likelihood of developing NSF suggests that there is a pooling of free gadolinium within the tissues, and eventually a critical concentration develops that triggers subsequent cellular and biochemical processes that lead to NSF. Or, that repeated stimulations of cellular events may be cumulative, even if the gadolinium is cleared. Recent studies by High et al. [18,19] have demonstrated accumulation of free gadolinium within skin through direct measurement of the gadolinium. Can high enough doses even with normal renal function cause gadolinium accumulation and disease? This is true of most drugs, from aspirin to intravenous saline. The question here is if cumulative Omniscan dose leads to free gad retention to different degrees dependent on delayed clearance at the time of administration, and can this occur, albeit more slowly in patients with moderate or even normal renal function? This simply remains unknown at this time. Studies (not yet published) in rats given very high doses of Gd-CAs through daily administrations have shown that skin lesions similar to NSF can be induced by Omniscan, and that relatively milder or early skin changes appear to be induced by even more stable agents. Although studies are ongoing, for now, there has been no data to show disease in normal patients, despite well over 150 million administrations of all Gd-CAs worldwide and over 20 million administrations specifically of Omniscan within the United States alone.

If renal failure leads to increased gadolinium accumulation through delayed excretion, can dialysis or alternative excretion pathways reduce NSF risk? To date, aggressive dialysis has not been shown effective [22]. In fact, dialysis is itself a high risk for morbidity and mortality and should never be advocated in patients who are not already dialysis dependent. Similarly, aggressive repeated dialysis after Gd-CA administration also may yield higher risk compared against no well documented therapeutic benefit. However, it has been suggested that delayed dialysis, in excess of several days, may be associated with higher risk of NSF, or worse disease. For example, our center data showed that all of our patients had mild NSF symptoms with no cases of joint contractures, decreased mobility, or death due to the NSF. This compares favorably compared against other reports of approximately over 30% severe disease with debilitating contractures [23]. Of note, our policy, even prior to knowing of the relationships to NSF, had been that all patients on dialysis were to have dialysis within 48 h after the contrast enhanced MRI. This policy had been in place as a matter of logical sense regarding the need to use dialysis to eliminate drugs requiring renal clearance in these patients.

Although most Gd-CAs are completely dependent on renal filtration for clearance, two agents are partially cleared by hepatic uptake and excretion into bile. It remains uncertain as to the significance of this characteristic. The benefits of this pharmacodynamic property has been questioned in one agent (MultiHance™) where hepatic clearance is estimated at 3% in patients with normal hepato-renal function, as compared to 50% in the other agent (Primovist™).

3. Lowering the risk of NSF

The data presented here taken in sum should allow us to now consider alterations in our standard for practice, to facilitate optimized use of diagnostic MRI balanced against minimized risk of inducing NSF.

3.1. Use higher stability Gd-CAs

The published evidence strongly supports a distinction should be made between agents. Use of more stable linear, and particularly the most stable agents, the cyclic Gd-CAs, should be advocated. The current cyclic agents include gadoteridol (ProHance™), gadobutrol (Gadovist™) and gadoterate (Dotarem™); only gadoteridol is available in the United States. The linear agents with no clear link to NSF include gadobenate dimeglumine (MultiHance™), gadoxetic acid disodium salt (Primovist™) and gadofosveset trisodium (Vasovist™); only gadobenate dimeglumine is available in the United States.

3.2. Control cumulative Gd-CA dose

Accepting the body of evidence supporting a dose-effect relationship leads to a need to consider controlling the cumulative dose to patients with severe renal insufficiency. Although we found that, on average, our NSF cases were associated with a triple cumulative dose of Omniscan [10], we can assume that higher doses of more stable agents would be required to induce disease. Thus, to leave a margin of safety, we have advocated no more than 0.3 mmol/kg of Gd-CA shall be given to patients with severe renal insufficiency (stage 4–5 disease). Any dose beyond this level should require a radiologist, in consultation with the referring clinician, to determine that the patient management would be negatively impacted if a contrast enhanced MRI were not performed. We have also instituted an aggressive dose minimization strategy for all patients. All patients now have the Gd-CA dose titrated to body weight, and moving towards the lowest possible dose while still preserving the diagnostic quality of the examination. Due to limited access to the full range of Gd-CAs in the United States, we have opted to use a linear agent that has higher relaxivity, which has then allowed preservation of image enhancement for most studies at a concentration of 0.05 mmol/kg.

3.3. Dialysis

As already discussed, aggressive dialysis may be harmful, but dialysis as soon as possible after Gd-CA administration is logical, if not yet supported by definitive data. We have modified our policy from dialysis within 48 h, reducing this to 36 h. We now screen patients at the time of MRI scheduling and determine when patients are scheduled for dialysis in order to have the MRI booked on the same day for the majority of patients.

3.4. Documentation

It has become incumbent upon all institutions to document what you are doing to minimize NSF risk. Documentation should include a screening questionnaire for renal disease, recognizing that the vast majority, if not all, outpatients with severe renal disease will provide this information, particularly those patients on dialysis. For in-patients, we now require an estimated GFR be obtained prior to the examination. These findings are noted in the medical records for the patient. We also note in the medical record, as part of the MRI report, the patient weight, the amount and the type of contrast agent used for the study. The prior administrations and cumulative dose is also calculated. A limitation here is in cases where patients may have had studies using Gd-CAs at other centers. Until a more centralized system for individual medical records is in place, although imperfect, we must rely on patient screening for this information.

4. Informed consent

As part of the informed consent process, where risks and benefits of the procedure and alternative procedures must be discussed with the patient, the following represents the major considerations for the practicing radiologist. Here we must consider the bigger picture, not just NSF. In the balance must be weighed the harm in not doing an optimized diagnostic test versus the potential risk of NSF. Contrast enhanced MRI has been firmly established as the most sensitive and specific diagnostic test for a range of diseases and organ systems. This includes evaluation of diseases ranging from tumors and inflammatory or infectious diseases in tissues ranging from brain to liver. In addition, we must consider what alternative tests entail, not only in regards to relative diagnostic sensitivity and specificity, but also in regards to relative safety and risks for morbidity and mortality.

Published evidence suggests that radiologists are not as well informed as we should be in regards to risks associated with our imaging procedures. This has been established in studies addressing radiologists knowledge of radiation risks associated with CT scanning [24,25] and iodine based contrast agents (I-CA) used in CT scanning [26].

So what are the risks associated with CT? First, let us consider radiation. The National Academy of Science (NAS) has estimated that a single 10 mSv dose to the body, as would be associated with the typical single pass abdominal CT scan, would lead to a life-time attributable risk of 1 lethal malignancy for every 1000 patients, considering the general population [27]. While the odds ratio would fall for older patients, the malignancy incidence would rise for younger patients, in excess of 1 in 100. The incidence estimated, using the linear attributable risk model applied by the NAS, predicts that the incidence climbs proportional to the number of scans, or the number of scanning passes as used in a multi-phase enhanced scan.

What about the risks associated with I-CA [28]? The risk for contrast induced nephropathy (CIN) has been well characterized in multiple large long-term studies, although mostly for arterial administrations related to cardiovascular examinations [29–31]. However, more recent studies have shown that CIN is a risk for patients receiving iodinated contrast for CT scans [32–34]. The patients at risk include those with moderate insufficiency (GFR <60 ml/min), diabetes, advanced age, congestive heart failure, dehydration, or other nephrotoxic drugs. In addition, even patients with apparently normal range GFR but who are acutely ill, as noted in a study of ICU patients, are at risk of CIN. Incidence rates of CIN for patients with risk factors receiving contrast enhanced CT studies have been reported between 9–18% [33], with irreversible renal disease in 4.8%. The odds ratio of mortality in patients with CIN has been measured at 5.5 (associated with a 37% 1-year mortality incidence) versus patients controlled for comorbid factors and exposed to I-CM but who did not develop CIN [31]. Although studies have mostly looked at patients with arterial administrations of contrast, we may presume that once CIN has been induced the outcomes of disease are similar regardless of the initial route of contrast administration.

When addressing individual patients, individual risks and benefits must be weighed. If it has been determined that the best diagnostic test is a contrast enhanced MRI in a patient with renal dysfunction, and a CT study represents the other potential diagnostic method, then relative risks should be considered. In patients with moderate to severe renal disease not on dialysis, current data indicates that iodinated contrast and CIN has greater associated risks, with potential for inducing permanently reduced renal function, need for dialysis, and mortality. In dialysis patients, the differential considerations should be swayed more heavily in favor of the best test required to manage the patient. In this subset it may be argued that the patients receiving I-CA will not suffer the consequences of renal insult, since they are already on dialysis. However, there are no reports specifically looking at long-term outcomes of these patients after I-CA administration. In acutely ill patients, as in those referred from the ICU, evidence suggests that MRI would be the safer choice regardless of renal function.

5. Summary

I have reviewed our current understanding of NSF and laid out the major considerations for an optimized approach to continued use of MRI for patients, even in the setting of severe renal insufficiency. As we continue to learn more about Gd-CA pharmacodynamics and the cellular basis of NSF we will likely require continued tuning of our optimized methodologies. Based on our current appreciation of the patterns of this disease, and the relative benefits and risks associated with alternative contrast

enhanced CT imaging, I feel we can, for now, offer a strategy that allows us to minimize the risks for developing NSF while maximizing the potential diagnostic yield for optimal patient management.

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