Intravenous gadolinium-based contrast agents (GBCAs) are commonly used for MRI to aid in the detection, characterization, and staging of disease. Although there have been millions of doses administered to patients since their introduction in 1988, there have been relatively few serious and life-threatening events. Despite warnings on package inserts, prior screening for chronic kidney disease (CKD) was widely thought to be unnecessary and was not considered the standard of care, and GBCAs were often administered at doses beyond those approved by regulatory agencies, especially for MR angiography (MRA), and even for some x-ray based imaging procedures.

The first patients with nephrogenic systemic fibrosis (NSF), were identified in 1997 and reported in 2000, but it was another six years before anyone showed a connection between NSF and GBCAs. Though GBCA-enhanced MRI is still considered to be safe for the majority of patients, the emergence of an association between GBCAs and NSF has led to a reassessment of the risks of contrast-enhanced MRI in patients with compromised renal function. It has also led the medical community to ask, “Why did it happen and what have we learned?”

A prolonged lag time between the introduction of a new pharmaceutical agent and the identification of an association with a serious adverse drug reaction (sADR.) is not unusual, and half of all notifications for sADRs were disseminated more than seven years after approval of the relevant pharmaceutical product by the Food and Drug Administration (FDA). This is also not without precedence in the field of medical imaging, and in the case of GBCAs, it appears that a confluence of factors conspired to cause the lag between their introduction for clinical use and identification of an association with NSF. Relevant factors might include the perceived advantage compared with iodinated agents in the context of CIN (contrast induced nephropathy) in renal compromised patients, the development of contrast-enhanced MRA requiring high doses of GBCA in early implementations, the clinical environment in which many of the scans were performed with limited physician engagement, poor record keeping, an imperfect pharmacovigilance infrastructure, and possibly changes in dialysis regimens. On the other hand, it should not be surprising that a connection between a widely used class of pharmaceutical agents employed by radiologists and a newly discovered, rare, and difficult to diagnose disease known primarily in the dermatology community would go unnoticed for years. Even the Centers for Disease Control (CDC) was unable to “connect the dots”.

There are fewer than 500 cases of NSF reported in peer review literature, and most of the cases are reported from a limited number of institutions the US. Definitive diagnosis of NSF usually requires consistent clinical and pathological features, and some suspect there is under-reporting. A growing body of evidence suggests that severe forms of NSF occur only in patients with acute kidney injury (AKI) or severe to end-stage chronic kidney diseases (CKD), usually on dialysis. However, most “high risk” patients do not develop NSF following GBCA exposure, and the number of new cases of NSF has dropped precipitously since 2007. Cause and effect and pathophysiology have not yet been firmly established, and issues concerning patient co-factors (triggering agents), dose and cumulative dose relationships, tissue deposition, pediatric patients, relative risks of various GBCAs, in vivo stability, screening, and treatment are still being clarified.

NSF has had profound consequences for many of the effected patients and families, and its appearance has served as a tragic reminder about the level of caution and vigilance that must be incorporated into the practice of medicine. If nothing else, it has spurred a more judicious use of GBCAs, the development and refinement of MRI (especially MRA) techniques that obviate the need for intravenous GBCAs, and research into the basic mechanisms underlying contrast agent pharmacology and toxicity that should lead, ultimately, to even safer and more effective products.