

## **Gadolinium-induced nephrogenic systemic fibrosis: the rise and fall of an iatrogenic disease.**

### **Abstract:**

In 2006, nephrologists in Denmark unexpectedly identified chronic kidney disease (CKD) patients with a new syndrome, nephrogenic systemic fibrosis (NSF). Subsequently, 1603 NSF patients were reported to the Food and Drug Administration. Sixty hospitals in the USA account for 93% of these cases, and two hospitals in Denmark account for 4% of these reports. We review Denmark's identification and subsequent rapid eradication of NSF. **METHODS.:** NSF reports from clinicians, the Danish Medicines Agency (DMA) and gadolinium-based contrast agents (GBCAs) manufacturers were reviewed (2002-11). **RESULTS.:** In 1994, the DMA approved a non-ionic linear GBCA, gadodiamide (0.1 mmol/kg), for magnetic resonance imaging (MRIs), with a renal insufficiency contraindication. In 1996, 0.3 mmol/kg dosing received DMA approval. In 1998, the DMA removed renal contraindications. In 1997 and 2002, radiologists at Skejby Hospital and Herlev Hospital, respectively, began performing gadodiamide-enhanced magnetic resonance angiography scans (0.3 mmol/kg) of CKD patients. In 2005, Herlev clinicians requested assistance in evaluating etiological causes of NSF occurring among 10 CKD patients who had developed NSF. This investigation, focusing on infectious agents, was inconclusive. In 2006, Herlev clinicians reported that of 108 CKD patients who had received gadodiamide-enhanced MRI, 20 had developed probable NSF. Herlev radiologists voluntarily discontinued administering gadodiamide to all patients and no new NSF cases at Herlev Hospital developed subsequently. After meeting with Herlev radiologists, Skejby radiologists also discontinued administering gadodiamide to all patients. In 2007, the European Medicines Agency and the DMA contraindicated gadodiamide administration to CKD patients. In 2008, in response to these advisories, radiologists at the other 36 Danish hospitals discontinued administering gadodiamide to all patients, following on practices adopted at Skejby and Herlev Hospitals. In 2009, clinicians at Skejby Hospital reported that a look-back survey identified 33 CKD patients with NSF developing after undergoing GBCA-enhanced MRIs between 1999 and 2007. In 2010, an independent review, commissioned by the Minister of Health, concluded that the DMA had erred in rescinding gadodiamide's renal insufficiency contraindication in 1998 and that this error was a key factor in the development of NSF in Denmark. In 2011, three NSF cases associated with macrocyclic GBCA-associated NSF and three NSF patients with Stages 3 and 4 CKD disease from Skejby Hospital were reported. **CONCLUSION.:** A confluence of factors led to the development and eradication of NSF in Denmark.