Nephrogenic Systemic Fibrosis: Suspected Causative Role of Gadodiamide Used for Contrast-Enhanced Magnetic Resonance Imaging

Peter Marckmann,* Lone Skov,† Kristian Rossen,‡ Anders Dupont,§ Mette Brimnes Damholt,* James Goya Heaf,* and Henrik S. Thomsen‖

*Departments of *Nephrology and ‖Diagnostic Radiology, Copenhagen University Hospital at Herlev, Herlev, Departments of †Dermatology and ‡Pathology, Copenhagen University Hospital at Gentofte, Hellerup, and §Faculty of Health Sciences, Copenhagen University, Copenhagen, Denmark*

Nephrogenic systemic fibrosis is a new, rare disease of unknown cause that affects patients with renal failure. Single cases led to the suspicion of a causative role of gadodiamide that is used for magnetic resonance imaging. This study therefore reviewed all of the authors' confirmed cases of nephrogenic systemic fibrosis ($n = 13$) with respect to clinical characteristics, gadodiamide exposure, and subsequent clinical course. It was found that all had been exposed to gadodiamide before the development of nephrogenic systemic fibrosis. The delay from exposure to first sign of the disease was 2 to 75 d (median 25 d). Odds ratio for acquiring the disease when gadodiamide exposed was 32.5 (95% confidence interval 1.9 to 549.2; $P < 0.0001$). Seven (54%) patients became severely disabled, and one died 21 mo after exposure. No other exposure/event than gadodiamide that was common to more than a minority of the patients could be identified. These findings indicate that gadodiamide plays a causative role in nephrogenic systemic fibrosis.

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Since 1997, a total of approximately 200 cases of nephrogenic systemic fibrosis (NSF), previously known as nephrogenic fibrosing dermopathy, have been reported worldwide (1,2). The appearance of this new and serious disease has triggered considerable interest as to possible causative factors, including newly introduced clinical practices. However, until now, the eliciting factor(s) has not been identified.

Mendoza *et al.* (3) recently reviewed the clinical picture of NSF. The typical patient is middle-aged and has ESRD. Most but not all are on regular dialysis treatment. The typical course begins with subacute swelling of distal parts of the extremities and is followed in subsequent weeks by severe skin induration and sometimes anatomic extension to involve thighs, antebrachium, and lower abdomen. The skin induration may be aggressive and associated with constant pain, muscle restlessness, and loss of skin flexibility. In some cases, NSF leads to serious physical disability, including wheelchair requirement. NSF initially was observed in and thought to affect solely the skin (thus the initial term nephrogenic fibrosing dermopathy), but more recent patient reports have demonstrated that several organs may be involved. Organ involvement may explain the suspected increased mortality of patients with NSF (3). There is no established treatment for NSF, but some cases have been reported to improve after kidney transplantation, and others seem to have been treated successfully with extracorporeal photopheresis (4).

At the department of nephrology, Copenhagen University Hospital at Herlev, we became aware of a formerly unknown skin disease among our patients with ESRD during 2002 through 2005. Skin biopsies supported the clinical suspicion of NSF. Some of the case stories strongly indicated that the skin changes were elicited by contrast-enhanced magnetic resonance imaging (MRI). Since late 2001, we have used this method frequently for patients with ESRD, in particular for description of iliac and lower limb arteries before kidney transplantation (5). During the past 5 to 10 yr, many other nephrology centers around the world increasingly have used contrast-enhanced MRI because of the lower nephrotoxic potential of extracellular MRI agents compared with iodinated contrast media (6). On the basis of our suspicion, we decided to make a review of all NSF cases with a special focus on exposure to contrast-enhanced MRI.

Materials and Methods

During August 2005 through May 2006, we identified all confirmed cases of NSF in our nephrology department. Each case was reviewed thoroughly with respect to clinical history and exposure to contrast-enhanced MRI. We also checked for other extraordinary exposures/events within the 6 mo before the first sign of NSF. The other exposures/events for which we checked were exposure to iodinated contrast media, scintigraphy, intravenous iron therapy, bacteremia, infection that required antibiotic therapy, thrombosis, and surgery. Patients were considered to have NSF only when the clinical course, the dermatologic findings, and the skin histology all were indicative of NSF

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Address correspondence to: Dr. Peter Marckmann, Department of Nephrology, Copenhagen University Hospital at Herlev, DK-2730 Herlev, Denmark. Phone: +45-44883634; Fax: +45-44884615; E-mail: peter.marckmann@dadlnet.dk

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as agreed unanimously by a panel composed of a clinician (P.M.), a dermatologist (L.S.), and a pathologist (K.R.).

Statistical Analyses

The odds ratio for developing NSF depending on gadodiamide exposure was calculated from our best estimates of the number of patients who had ESRD and had or had not been exposed. We used GraphPad Instat, version 3.05 (GraphPad Software, San Diego, CA; www.graphpad.com) for this purpose.

Results

Up to June 12, 2006, we identified 13 patients (eight women, five men) with NSF. Skin histology ($n = 13$) varied from subtle proliferation of dermal fibroblasts consistent with NSF to frank NSF as described by Cowper *et al.* (7) and Swartz *et al.* (8).

Mean age at first sign of NSF was 50 yr (range 33 to 66 yr). All patients had ESRD, but they differed with respect to primary renal disease (Table 1). NSF proceeded to severe disability (contractures, loss of physical abilities, and deterioration of overall clinical state) in seven cases. One of the severely disabled patients (patient 4) died from cachexia and pneumonia 20 mo after the first sign of NSF. The remaining six patients were more mildly affected (leg swellings and skin induration with/without local pain). One patient had a seemingly total, spontaneous remission of a mild disease while continuing on regular hemodialysis therapy (patient 7).

All 13 patients had been exposed to contrast-enhanced MRI with gadodiamide (0.5 mol/L Omniscan; GE Health Diagnostics, Amersham, U.K.) before the appearance of NSF symptoms. The median time from gadodiamide exposure to first medically recorded note of clinical signs that were indicative of NSF (*e.g.*, development of skin rash/induration, unexplained swollen legs, leg pain) was 25 d (range 2 to 75 d; Table 2). None of the other extraordinary exposures/events was common to more than seven patients during the 6-mo period that preceded NSF debut.

The amount of gadodiamide that was used for the seeming NSF-eliciting MRI procedure varied between patients from 9 to 25 mmol (Table 2). The average contrast volume was 18.5 mmol (SD 5.5 mmol). We could not demonstrate any association between dosage and NSF severity.

Our patients with NSF belonged to different treatment categories at the time of gadodiamide exposure, including regular hemodialysis therapy ($n = 7$), regular peritoneal dialysis therapy ($n = 1$), and conservative treatment ($n = 5$). One patient had late failure of a renal graft (patient 1), and one patient had a recently transplanted yet poorly functioning kidney graft (patient 11).

Six of the 13 patients had been exposed to up to 25 mmol of gadodiamide earlier, apparently without developing NSF symptoms. Two patients were exposed to an additional infusion of gadodiamide after NSF had developed. The cumulative dose of gadodiamide varied from 11 to 63 mmol between patients.

Acidosis has been proposed as a causal co-factor in NSF pathogenesis (9). In our material, plasma bicarbonate was available from 12 patients (not available for patient 1) who had blood samples taken 0 to 36 d (median 14 d) before gadodiamide exposure. Mean plasma bicarbonate in these samples was 22.5 mmol/L (range 15 to 30 mmol/L; reference interval 22 to 29 mmol/L). Three patients had blood samples taken on the day of exposure. Their plasma bicarbonate levels were 18, 30, and 21 mmol/L (patients 8, 11, and 13, respectively).

From patient files of the Department of Diagnostic Radiology, we verified that a maximum of 370 of an estimated total of 800 to 1000 patients who had ESRD and attended our nephrology department during 2001 to 2006 had been exposed to gadodiamide. From a 2×2 contingency table (13 cases among 370 exposed, 0 cases among 430 to 630 unexposed), an odds ratio between 32.5 (95% confidence interval 1.9 to 549.2; $P < 0.0001$) and 47.6 (95% confidence interval 2.8 to 804.0) for having NSF when exposed was calculated.

Discussion

As described, we have seen an accumulation of the formerly unknown disease NSF among our patients with ESRD during the past 4 to 5 yr. NSF has appeared in parallel with our increased use of gadodiamide-enhanced MRI. The same parallelism is seen at the global level: The first reported NSF case was observed in 1997 (1). The first reports on the use of ga-

Table 1. Age, gender, primary renal disease, and clinical course of 13 patients with ESRD and nephrogenic systemic fibrosis[a]

Patient	Age (yr), Gender	Primary Renal Disease	NSF Clinical Picture
1	38, F	GN	Mildly disabled
2	63, F	GN	Mildly disabled
3	56, M	Hyp.art.	Severely disabled
4	47, M	GN	Severely disabled, deceased 20 mo after debut
5	55, F	PN	Severely disabled
6	33, F	Dysplasia renis	Severely disabled
7	66, M	GN	Local/minor symptoms, full remission
8	51, M	Diabetes	Severely disabled
9	57, M	Hyp.art.	Mildly disabled
10	51, F	GN	Severely disabled
11	47, F	Hyp.art.	Local/minor symptoms
12	38, F	GN	Local/minor symptoms
13	50, F	GN	Severely disabled

[a]GN, glomerulonephritis; Hyp.art., hypertensive nephropathy; NSF, nephrogenic systemic fibrosis; PN, chronic pyelonephritis.

Table 2. Date of gadodiamide exposure, amount of infused gadodiamide, renal function at time of exposure, and time span from exposure to first medically recorded sign of nephrogenic systemic fibrosis in 13 patients with NSF[a]

Patient	Exposure Date	Exposure (mmol)	Renal Function	Time Span to First Sign of NSF (d)
1	September 18, 2002	20	eGFR 7 ml/min	7
2	December 16, 2002	20	HD	2
3	December 5, 2003	23	HD	18
4	February 11, 2004	9	PD	30
5	June 29, 2004	25	HD	62
6	December 1, 2004	21	HD	25
7	January 17, 2005	15	eGFR 7 ml/min	29
8	April 11, 2005	17	HD	21
9	June 24, 2005	25	HD	6
10	July 15, 2005	18	HD	46
11	August 17, 2005	15	eGFR 6 ml/min	75
12	September 14, 2005	11	eGFR 5 ml/min	31
13	January 24, 2006	25	eGFR 5 ml/min	7

[a]eGFR, estimated GFR; HD, hemodialysis; PD, peritoneal dialysis.

dodiamide in humans appeared in 1993 (10), and the first Medline-indexed paper describing the use of gadolinium (Gd)-enhanced MRI in renal patients was published in 1997 (11).

All of our patients with NSF had been exposed to gadodiamide before their first sign of NSF. The median time from exposure to first medically recorded note of NSF was 25 d. In some cases, the delay was short and the link between exposure and NSF seemed obvious. However, in others, NSF developed less dramatically, had a more insidious course, and was diagnosed later. Importantly, we have not observed a single case of NSF among patients who were not exposed to gadodiamide. Consequently, the odds ratio for acquiring NSF when exposed is high and statistically highly significant in our material.

Our patients with NSF were younger (mean age 50 yr) compared with our average patient with ESRD (mean age 65 yr). Also, they all were in a relatively good clinical condition before the development of NSF. Most of them were potential kidney transplant candidates and had been referred for gadodiamide-based MR arteriography of iliac and lower limb vessels, which has been part of our routine pretransplantation examination program since late 2001.

In a recent case report, Grobner (9) was the first to propose that MR contrast media that contain Gd might be a trigger of NSF. He reported that five of nine hemodialysis patients who were exposed to a Gd-based contrast medium developed NSF within 2 to 4 wk. The contrast medium that was used in Grobner's patients also was gadodiamide (Thomas Grobner, personal communication, April 2006). According to Grobner, acidosis might be an essential co-factor in the pathogenesis of NSF. Although we did not have blood samples from the day of gadodiamide exposure except in three cases, our finding of an average plasma bicarbonate of 22.5 mmol/L shortly before exposure does not support this hypothesis.

The evidence outlined above has led us to suspect gadodiamide as a causal factor in NSF. Consequently, we stopped further routine use of gadodiamide-based MRI in patients with ESRD at Copenhagen University Hospital at Herlev from March 21, 2006, until further notice. We have not seen any new NSF cases after that date.

Gadodiamide belongs to the group of extracellular contrast media that are used for MRI. It is a non–tissue-specific and nonionic low-osmolar (650 mOsm/kg) agent (12). Gadodiamide is almost exclusively excreted renally and therefore has a markedly prolonged half-life in patients with renal failure, including dialysis patients. The gadodiamide half-life of healthy volunteers is 1.3 h, of patients with end-stage renal failure is 34.3 h, of hemodialysis patients is 2.6 h, and of peritoneal dialysis patients is 52.7 h (13). It previously was considered a safe agent, even in patients with renal failure (6). The molecular structure of chelate-binding (diethylenetriaminepentaacetic acid-bis-methylamide) Gd is linear. Gadodiamide formulation differs from most other non–tissue-specific extracellular MRI agents by having an excess chelate (12 mg/ml). Whether this could have an impact on NSF development is not known. Alternatively, NSF could be a toxic reaction to free Gd that is liberated from gadodiamide. Free Gd is highly toxic, in particular in its ionic form (Gd^{3+}) (14). Gadodiamide leaves two to four times more Gd in the bone than gadoteridol in patients with normal renal function (15). Because of the longer half-life of contrast Gd-based media in patients with ESRD, we speculate that Gd liberation might be causing NSF.

It is important to note that several of our patients with NSF had been exposed to gadodiamide earlier without developing signs of NSF. This observation suggests that gadodiamide was a necessary but not a sufficient cause of NSF. Certain other factors must have played a role, but we have not been able to identify any such co-factor.

Conclusion

NSF is a new, rare, and serious disease that occurs primarily in middle-aged patients with ESRD. We have seen an accumulation of NSF cases in our department, which seems related to

our frequent use of gadodiamide for MRI. Our review of 13 NSF cases has convinced us that we should avoid the use of gadodiamide in patients with ESRD until the suspicion of a causal link has been investigated further. We recommend that others consider the same and systematically look for signs of NSF in patients who have ESRD and were exposed previously to gadodiamide and other Gd-based contrast media.

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