Journal of the American College of Cardiology
© 2009 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 53, No. 18, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2008.12.061

STATE-OF-THE-ART PAPER

Nephrogenic Systemic Fibrosis

Pathogenesis, Diagnosis, and Therapy

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Nephrogenic systemic fibrosis (NSF) is a newly recognized disorder occurring exclusively in patients with renal failure. Exposure to gadolinium-based magnetic resonance (MR) contrast media has been associated with subsequent development of NSF. Nephrogenic systemic fibrosis is characterized by skin induration preferentially affecting the extremities. In addition, involvement of internal organs occurs, which leads ultimately to death. Skin biopsy is important for confirmation of the diagnosis. The main therapeutic goal is restoration of renal function. To reduce the risk of NSF, renal function must be determined before exposure to gadolinium-containing MR contrast agents. Gadolinium-based MR contrast media should be avoided in the presence of advanced renal failure with estimated glomerular filtration rate below 30 ml/min/1.73 m^2, unless the diagnostic information is essential and not available with noncontrast magnetic resonance imaging techniques. The recommended dose of contrast agent should not be exceeded. In addition, a sufficient period of time for elimination of the contrast agent from the body should be allowed before readministration of the contrast agent. (J Am Coll Cardiol 2009;53: 1621–8) © 2009 by the American College of Cardiology Foundation

Nephrogenic systemic fibrosis (NSF) is a new disorder exclusively observed in patients suffering from renal failure. Because it was initially assumed that the disorder was limited to the skin, the term "nephrogenic fibrosing dermatopathy" was chosen (1). The recognition of the disorder's systemic nature with fibrotic changes in various organ systems led to the renaming of the disease as nephrogenic systemic fibrosis (2). As of May 2008, 215 cases have been described in a U.S. registry (3). Approximately 80 cases are cumulatively reported within European patients; the reports mainly originated from Austria and Denmark. A registry for Germany was opened in the summer of 2007 (4). Gadolinium-containing magnetic resonance (MR) contrast agents seem to be associated with the disease development (5,6). This overview summarizes the current knowledge about the pathogenesis, diagnosis, and therapy in order to increase awareness of this new syndrome.

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Manuscript received August 11, 2008; revised manuscript received December 3, 2008, accepted December 8, 2008.

Epidemiology

Nephrogenic systemic fibrosis was only recognized after large numbers of patients were given gadolinium-based contrast agents. Before 1997 the disease was not reported. There was a change in clinical practice and use of high-dose gadolinium-enhanced magnetic resonance angiography (MRA) for improved imaging. Gadolinium-enforced MRA was used preferentially in patients with renal failure to avoid iodinated (X-ray) contrast agents. The increasing cumulative dosage of these gadolinium-containing contrast agents might have contributed to the development of NSF. Nevertheless, the combination of rapid, higher-than-approved doses of contrast agents and the clustering of cases were probably important factors that likely led to the recognition of this new syndrome.

Additional unknown risk factors might play a role in facilitating NSF. Nephrogenic systemic fibrosis is diagnosed with equal frequency in men and women and affects patients of all ages and ethnicities (7–9). In a cohort of American dialysis patients, the frequency was 3 cases in 467 patients observed over 18 months, resulting in an estimation of 4.3 cases/1,000 patient-years (10). The risk of triggering the disorder in these patients through a gadolinium application with different gadolinium-based agents was calculated to be 2.4% (10).

A recent European study found NSF in 18 (18%) of 102 patients with stage 5 chronic kidney disease (CKD) with and without dialysis after exposure to the gadolinium

Abbreviations and Acronyms

AKI = acute kidney injury
CKD = chronic kidney disease
FDA = Food and Drug Administration
GFR = glomerular filtration rate
MRA = magnetic resonance angiography
MRI = magnetic resonance imaging
NSF = nephrogenic systemic fibrosis

derivate gadodiamide (Omniscan, GE Healthcare Medical Diagnostics, Amersham, United Kingdom). Most of the patients in this study received high doses of gadodiamide (typically approximately 0.3 mmol/kg) for angiography (11). Another study using Gadoteridol (ProHance, Bracco Diagnostics, Milan, Italy) in 141 patients receiving long-term hemodialysis found no NSF (12). A further study found discrete clinical signs of NSF in 30% of hemodialysis patients after gadopentetate dimeglumine (Magnevist, Bayer Schering Pharma AG, Berlin, Germany) exposure. However, skin biopsies were not used to confirm the diagnosis of NSF in this patient cohort (13). Prince et al. (14) assessed the incidence of NSF in 2 large medical centers in the U.S. Of 83,121 patients who received gadolinium-based contrast agents, 15 (0.02%) developed NSF. All of them got a high dose of the contrast agent that exceeded the standard dosage. Most of them suffered from acute renal failure at the time of administration; 8.4% of all patients with acute renal failure receiving gadolinium developed NSF. Wertman et al. (15) recently calculated the benchmark incidence of NSF with data from 4 large U.S. health care centers. The benchmark incidence of NSF ranged from 1 of 2,131 patients to 1 of 65,000 patients. This study confirmed previous findings showing that only patients with severe renal impairment and/or stage 4/5 CKD develop NSF.

Renal failure

According to current knowledge, impaired renal function seems to be a conditio sine qua non for NSF. Nephrogenic systemic fibrosis was described in patients with stage 4 and 5 CKD without dialysis, patients requiring dialysis (hemodialysis and peritoneal dialysis), patients who had received renal transplants, as well as patients with acute kidney injury (AKI).

CKD is defined as either kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for ≥ 3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies (16). Chronic kidney disease is classified into 5 stages according to the GFR. Stage 1 CKD is diagnosed as kidney damage with normal or increased GFR (>90 ml/min/1.73 m^2); stage 2 is diagnosed as kidney damage with a GFR of 60 to 89 ml/min/1.73 m^2. Stage 3 CKD is defined by a GFR of 30 to 59 ml/min/1.73 m^2, and stage 4 CKD is defined by a GFR of 15 to 29 ml/min/1.73 m^2. Stage 5 CKD is defined as established kidney failure with a GFR <15 ml/min/1.73 m^2 or permanent dialysis therapy (16).

The extent of renal failure that triggers NSF is not known. There are only a few cases with a GFR >15 ml/min/1.73 m^2 reported. To the authors' best knowledge, there is no case with a reported GFR >30 ml/min/1.73 m^2. Although severe renal impairment seems to be a major condition, caution should be advised in recommending a safe range for gadolinium exposure above a specific GFR until further details of the disease are elucidated.

Gadolinium exposure

The association between the occurrence of NSF and preceding gadolinium exposure within the context of an MR study was first demonstrated in 2006 by Grobner (5) and his team in Austria in 5 patients and by Marckman et al. (6) in 19 patients from Denmark. An evaluation of an American patient cohort indicated gadolinium exposure for patients before the manifestation of NSF. Gadolinium was found in the skin of the patients (17,18). This association led to warnings by the Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products regarding the use of gadolinium-containing contrast agents in patients suffering from renal failure (19,20).

In normal renal function, free gadolinium is removed by the kidney with a half-life of approximately 2 hours. In impaired renal function, this half-life is significantly longer. Two consecutive hemodialysis sessions remove approximately 93% of the gadolinium, whereas the peritoneal dialysis is significantly less effectively and only removes approximately 75% of the gadolinium after 5 days (21–23).

A recent meta-analysis by Agarwal et al. (24) demonstrated a significant association between gadolinium-based contrast agent exposure and NSF. Nevertheless, at the time of this writing it cannot be decided whether or not the risk of occurrence of NSF differs for the various gadolinium-containing contrast agents (Table 1). The majority of patients with NSF cases had a prior administration of gadodiamide (Omniscan, GE Healthcare Medical Diagnostics), although the product is used in only approximately 15% of magnetic resonance imaging (MRI) studies worldwide (25). It has been hypothesized that the occurrence of NSF after the application of gadodiamide is related to the lower stability and increased occurrence of toxic free gadolinium in the gadodiamide complex (26,27). Nevertheless, in some of the studies the gadodiamide dose was very high; thus it has to be considered that the high dosage rather than gadodiamide itself facilitated the development of NSF in these cases (5,6,28–31). According to the FDA, no MR contrast agent can principally be regarded as safe, because NSF has also been observed after exposure to other gadolinium-containing contrast agents in the U.S. (19): Gadopentetane dimeglumin (Magnevist, Bayer Schering Pharma AG), gadobenate dimeglumin (MultiHance, Bracco Diagnostics), gadodiamide (Omniscan, GE Healthcare Medical Diagnos-