Gadolinium and the Development of Nephrogenic Fibrosing Dermopathy

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INTRODUCTION

Recently, it has been suggested that there may be a link between gadolinium (Gd) contrast agents and the development of nephrogenic fibrosing dermopathy (NFD), also known as nephrogenic systemic fibrosis (NSF). Reports of NSF/NFD in the current literature have occurred in renal insufficiency patients who received high doses of gadolinium (triple doses) for magnetic resonance angiography (1).

NSF/NFD is a scleroderma-like disease that causes thickened and fibrotic skin with hyperpigmentation. Limited range of motion and fibrosis of body organs are commonly associated symptoms of the disease. Since 1997, the national NFD registry has reported over 200 cases; there are no documented cases before 1997. All patients have had renal failure, but NSF/NFD development has been independent of age, gender, dialysis history, or kidney transplant status (2,3). Grobner *et al.* reported nine cases of NSF/NFD in which patients had been administered Gd-DTPA before the disease developed (1). In this study, we have retrospectively analyzed our database of renal insufficiency patients presenting to MRI and compared them to patients who developed NSF/NFD at our institution.

MATERIALS AND METHODS

IRB approval for this study was obtained according to our institutional guidelines. All patients who were diagnosed with NSF/NFD between 2003 and 2006 were identified and analyzed. In addition, inpatients presenting to MRI with renal insufficiency (estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2) between June 2005 and July 2006 who did not develop NSF/NFD were also identified and analyzed. For all patients, demographics, time of disease onset (if applicable), date and type of contrast-enhanced (CE) MRI/MRA, contrast agent, contrast dose, eGFR, albumin, creatinine (Cr), red blood cell morphology, and major infection/thrombosis/surgery ("pro-inflammatory" events) were noted. Common characteristics of NSF/NFD patients were identified. The prevalence of the disease at our institution was calculated. Average eGFR, number of MR exams, and number of pro-inflammatory events (infection/thrombosis/surgery) for the non-NSF/NFD patients and NSF/NFD patients were plotted.

RESULTS AND DISCUSSION

Between 2003 and 2006, thirteen patients were identified with biopsy-proven NSF/NFD (age range = 17 – 69 years; five women and eight men). All thirteen of these patients were inpatients at the time of their CE-MRI/MRA and all patients had received an injection of Omniscan (gadodiamide) contrast agent. NSF/NFD patients had a CE-MRI/MRA between 14 and 180 days prior to NSF/NFD diagnosis. All 13 NSF/NFD patients also had a major pro-inflammatory event (major infection/thrombosis/surgery), abnormal red blood cell morphology, and low albumin (<3.9 g/dl). The dose of gadolinium given to patients was 0.1 mmol/kg in 3/13 patients, 0.2 mmol/kg in 4/13 patients, and 0.3 mmol/kg in 6/13 patients. For creatinine values, 7/13 patients had a Cr = >4.0 mg/dl, 4/13 had a Cr = 2 to 4 mg/dl, and 2/13 had a Cr = <2.0 mg/dl. In 7/13 patients, eGFR was <15 ml/min/1.73 m^2; in 4/13 patients, eGFR was between 15 and 30 ml/min/1.73 m^2; and in 2/13 patients, eGFR was between 30 and 60 ml/min/1.73 m^2. No other apparent trends existed among the thirteen patients with NSF/NFD.

Between June 2005 and July 2006, there were 123 inpatients with renal insufficiency and a major pro-inflammatory event (infection/thrombosis/surgery) who received CE-MRI/MRA examinations. Six of these inpatients developed NSF/NFD, resulting in a prevalence of 5% within our population. Average eGFR for the 117 non-NSF/NFD patients was 29.0 ± 14.3 ml/min/1.73 m^2 and was 22.6 ± 17.7 ml/min/1.73 m^2 for the 13 patients with NSF/NFD (Figure 1). The difference in estimated GFR between the two groups of patients was statistically significant (p = 0.0004). The average number of MR exams was 1.52 ± 0.76 for the 117 non-NSF/NFD patients and 2.42 ± 0.67 for the 13 NSF/NFD patients (Figure 2). The difference in the number of MR exams between the two groups of patients was statistically significant (p = 0.0048). The average number of pro-inflammatory events was 1.47 ± 0.63 for the 117 non-NSF/NFD patients and 2.08 ± 0.67 for the 13 NSF/NFD patients (Figure 2). The difference in the number of pro-inflammatory events for the two groups of patients was statistically significant (p = 0.0014).

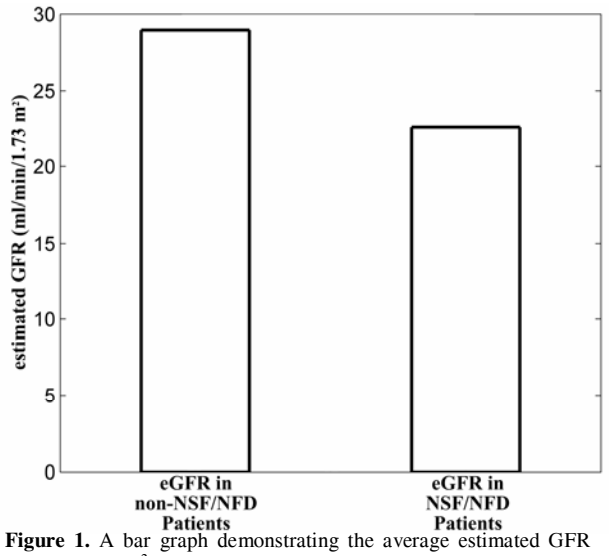

Figure 1. A bar graph demonstrating the average estimated GFR (ml/min/1.73 m^2) in 117 non-NSF/NFD patients and 13 NSF/NFD patients. The difference in estimated GFR between the two groups of patients was statistically significant (p = 0.0004).

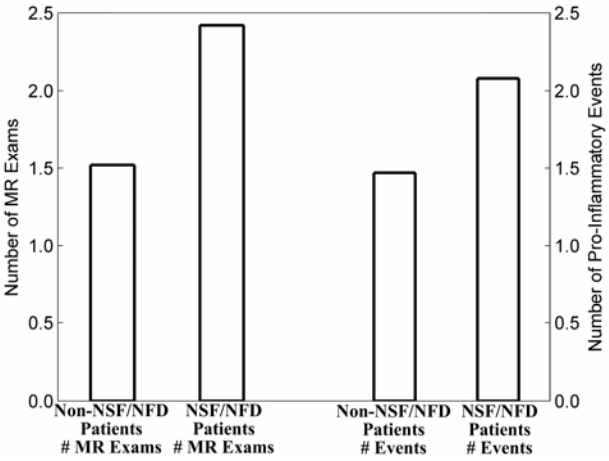

Figure 2. A bar graph demonstrating the average number of MR exams and average number of pro-inflammatory events (infection/thrombosis/surgery) in 117 non-NSF/NFD renal insufficiency patients and 13 NSF/NFD patients. The difference in the number of MR exams between the two groups of patients was statistically significant (p = 0.0048). The difference in the number of pro-inflammatory events between the two groups of patients was also statistically significant (p = 0.0014).

CONCLUSIONS

There is an apparent association between NSF and gadolinium exposure. Thirteen inpatients at our institution have developed NSF/NFD after receiving gadodiamide. All of these patients were in a "pro-inflammatory" state at the time of gadodiamide administration. Inflammatory processes, in addition to renal insufficiency and gadolinium exposure, may lead to the development of NSF. Our small cohort of patients also had abnormal red blood cell morphology and low albumin. Further studies are needed to evaluate the safety of gadolinium contrast use in renal insufficiency patients and to determine its role in the development of NSF/NFD.

REFERENCES

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