



Published in final edited form as:

Pediatr Radiol. 2014 February ; 44(2): 173–180. doi:10.1007/s00247-013-2795-x.

Pediatric nephrogenic systemic fibrosis is rarely reported: a RADAR report

Beatrice Nardone,

Department of Dermatology Northwestern University Feinberg School of Medicine, 676 N. Saint Clair St., Ste. 1600, Chicago, IL 60611, USA

Elise Saddleton,

Department of Radiology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Anne E. Laumann,

Department of Dermatology Northwestern University Feinberg School of Medicine, 676 N. Saint Clair St., Ste. 1600, Chicago, IL 60611, USA

Beatrice J. Edwards,

Department of Medicine, Division of General Internal Medicine and Geriatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Dennis W. Raisch,

VA Cooperative Studies Program Clinical Research Pharmacy, Albuquerque, NM, USA; University of New Mexico College of Pharmacy, Albuquerque, NM, USA

June M. McKoy,

Department of Medicine, Division of General Internal Medicine and Geriatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Steven Belknap,

Department of Dermatology Northwestern University Feinberg School of Medicine, 676 N. Saint Clair St., Ste. 1600, Chicago, IL 60611, USA; Department of Medicine, Division of General Internal Medicine and Geriatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Christian Bull,

Department of Dermatology Northwestern University Feinberg School of Medicine, 676 N. Saint Clair St., Ste. 1600, Chicago, IL 60611, USA

Anand Haryani,

Southern Illinois University School of Medicine, Springfield, IL, USA

Shawn E. Cowper,

Departments of Dermatology and Pathology, Yale School of Medicine, New Haven, CT, USA

Ali K. Abu-Alfa,

Division of Nephrology and Hypertension-American University of Beirut, Beirut, Lebanon; Section of Nephrology, Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA

Frank H. Miller,

dwest@northwestern.edu.

Conflicts of interest None.

Department of Radiology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Victoria Godinez-Puig,

Department of Dermatology Northwestern University Feinberg School of Medicine, 676 N. Saint Clair St., Ste. 1600, Chicago, IL 60611, USA

Vikas R. Dharnidharka, and

Division of Pediatric Nephrology, Washington University School of Medicine and St. Louis Children's Hospital, St. Louis, MO, USA

Dennis P. West

Department of Dermatology Northwestern University Feinberg School of Medicine, 676 N. Saint Clair St., Ste. 1600, Chicago, IL 60611, USA; Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Abstract

Background—Nephrogenic systemic fibrosis is a fibrosing disorder associated with exposure to gadolinium-based contrast agents in people with severely compromised renal function.

Objective—The purpose of this study was to determine the reported number of cases of nephrogenic systemic fibrosis in children using three distinct publicly available data sources.

Materials and methods—We conducted systematic searches of the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS), the International Center for Nephrogenic Systemic Fibrosis Research (ICNSFR) registry and published literature from January 1997 through September 2012. We contacted authors of individual published cases to obtain follow-up data. Data sets were cross-referenced to eliminate duplicate reporting.

Results—We identified 23 children with nephrogenic systemic fibrosis. Seventeen had documented exposure to gadolinium-based contrast agents. Six children had been reported in both the FAERS and the literature, four in the FAERS and the ICNSFR registry and five in all three data sources.

Conclusion—Nephrogenic systemic fibrosis has been rarely reported in children. Although rules related to confidentiality limit the ability to reconcile reports, active pharmaco-vigilance using RADAR (Research on Adverse Drug events And Reports) methodology helped in establishing the number of individual pediatric cases within the three major data sources.

Keywords

Gadolinium; Contrast media; Nephrogenic systemic fibrosis; Children; FAERS (FDA Adverse Event Reporting System); Clinical registry

Introduction

Nephrogenic fibrosing dermopathy was first noticed clinically in 1997. In 2000 a publication described 13 adults with end-stage renal disease who developed a scleromyxedema-like skin disorder [1]. Subsequent studies demonstrated systemic involvement leading to the current name, nephrogenic systemic fibrosis (NSF) [2-4]. Clinically the skin becomes thickened and tethered to the underlying tissue, resulting in reduced range of motion and contractures [5]. Internal organs, including the lungs, heart, dura mater and muscles, can be involved in the fibrosing process [6].

Gadolinium-based contrast agents are used to improve the detection and characterization of lesions during MRI and MR angiography. Gadolinium-based contrast agents can be classified based on structure, linear or cyclic, or charge, ionic or nonionic [7]. These characteristics can contribute to the agents' relative toxicity. Although gadolinium-based contrast agents are associated with a lower incidence of adverse events than iodinated contrast agents (ICAs) [8] and might be considered safer than iodinated contrast agents in people with renal dysfunction [9], the association between gadolinium-based contrast agents and nephrogenic systemic fibrosis, initially hypothesized in 2006, has significantly altered current practice [10].

Nephrogenic systemic fibrosis occurs exclusively in people with severely compromised renal function. This is precisely the population at risk for contrast-induced nephropathy associated with iodinated contrast agents [11]. Renal excretion is the primary elimination route for gadolinium-based contrast agents. In healthy individuals, the half-life of some agents may be only 1.3 h, whereas it can be prolonged to 10 h when the estimated glomerular filtration rate (eGFR) is 20-40 mL/min/1.73 m² and to more than 3 weeks in end-stage renal disease [12, 13]. The mechanism by which gadolinium promotes nephrogenic systemic fibrosis remains unknown; however it has been hypothesized that prolonged tissue exposure to gadolinium-based contrast agents, along with the presence of other factors such as inflammatory events, metabolic acidosis and erythropoietin exposure, might allow elemental gadolinium to separate from its ligand and disperse and deposit in tissue, promoting fibrosis [14]. The presence of gadolinium in tissue might be responsible for the occurrence of nephrogenic systemic fibrosis in susceptible children [12].

Although nephrogenic systemic fibrosis has been described in adults, very little is known about its epidemiology, especially in children [5, 15-23]. The aim of this project was to ascertain the number of cases of nephrogenic systemic fibrosis in children using three distinct data sources dating from Jan. 1, 1997, to Sept. 30, 2012.

Materials and methods

The Research on Adverse Drug Reactions and Reports (RADAR) project is a clinically based academic post-marketing surveillance program based at Northwestern University. The program systematically investigates and disseminates information describing serious and previously unrecognized adverse drug and device reactions; over 40 such reports have been generated since 1998. The overarching goals of the program are to identify, evaluate and disseminate reports on adverse drug and device reactions, thus improving patient safety [24].

After Northwestern University Institutional Review Board (IRB) approval, using RADAR (Research on Adverse Drug events And Reports) methodology [24, 25], we examined several data sources, including the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS), the International Center for NSF Research (ICNSFR) registry and published case reports. Pediatric patients are defined as 18 years and younger.

Food and Drug Administration Adverse Event Reporting System (FAERS)

The search period for FAERS was Jan. 1, 1997, to Sept. 30, 2012. Search terms included "nephrogenic systemic fibrosis," "nephrogenic fibrosing dermatopathy" and all U.S.-marketed generic and brand names for gadolinium-based contrast agents. Redacted narrative summaries for all 1,515 search matches were obtained through the Freedom of Information Act. Sorting by age and assessing for redundancy based upon gender, concurrent medical diagnoses and published articles mentioned in some of the reports, we determined the number of cases attributable to the pediatric age group. If age was not reported, further review was done to pinpoint pediatric versus adult cases.

International Center for Nephrogenic Systemic Fibrosis Research (ICNSFR)

ICNSFR data were retrieved from inception through Sept. 30, 2012. The ICNSFR is a voluntary international registry founded and maintained by Dr. Shawn Cowper, a dermatopathologist, who verifies each case for clinical and pathological consistency with nephrogenic systemic fibrosis and for uniqueness within the registry [26]. For this project, the ICNSFR provided age and date of onset of nephrogenic systemic fibrosis and date of biopsy for all known cases age 18 years and younger.

Published case reports

We conducted searches dating from January 1997 through September 2012 using PubMed, Embase and Cochrane Library databases. Search terms included “nephrogenic systemic fibrosis,” “nephrogenic fibrosing dermopathy,” “pediatrics” and “children.” Eight case-report authors were contacted directly for additional data, including exposure to gadolinium-based contrast agents and dose, as well as clinical outcomes. When the FDA report referenced a publication related to the case, we reviewed the narrative text from the FAERS MedWatch report with the author of the publication to reconcile the data. All cases were cross-referenced within and among data sources to identify redundant reports.

According to the current clinicopathological definition for the diagnosis of nephrogenic systemic fibrosis, major clinical criteria include: cutaneous patterned plaques, joint contractures, skin cobble-stoning and marked induration or *peau d'orange*, and minor criteria include cutaneous puckering or linear banding, superficial plaques or patches, dermal papules and, in people younger than 45 years, scleral plaques. The diagnosis of nephrogenic systemic fibrosis was based on recently published criteria as follows: if there is more than one major criterion the clinical diagnosis is highly consistent with nephrogenic systemic fibrosis; with one major criterion the diagnosis is suggestive of nephrogenic systemic fibrosis; with more than one minor criterion the diagnosis is consistent with nephrogenic systemic fibrosis [27].

Results

Forty reports were detected in the three data sources resulting in 23 non-redundant pediatric cases of nephrogenic systemic fibrosis, including 16 from the FAERS, 12 from the ICNSFR and 12 in the literature [5, 15-23, 28].

Of the 16 reports in FAERS, 1 individual was replicated 4 times, leaving 12 non-redundant cases. The ICNSFR registry retains secured patient identifiers locally in order to avoid redundancies within the database. Of the 12 reports in the literature, 3 involved multiple reporting, leaving 9 non-redundant cases.

Six of the non-redundant cases were in both the FAERS and the published literature and four in both the FAERS and the ICNSFR registry. Five non-redundant cases appeared in all three data sources.

Thirteen of the 23 non-redundant cases described herein were highly consistent with nephrogenic systemic fibrosis, 7 were consistent with NSF, and 3 were suggestive of NSF. These 3 cases suggestive of nephrogenic systemic fibrosis were found in the FAERS data set only.

Of the 23 non-redundant cases (mean age 13.6 years, range 6-18 years) 11 were boys, 3 girls. Gender was unreported in the remaining 9 cases.

Exposure to gadolinium-based contrast agents was reported in 74% of the children (17/23). All FAERS cases indicated previous exposure to gadolinium-based contrast agents because MedWatch reporting necessitates naming the agent for which the adverse event is being assessed. All nine children in the published literature had exposure to gadolinium-based contrast agents: seven children were documented in the original publication and two were discovered through author contact. Although ICNSFR registry inclusion does not require documented exposure to gadolinium-based contrast agents, exposure was confirmed in 5 of the 12 ICNSFR cases (note: one additional case was confirmed by another source to have had exposure to gadolinium-base contrast agents). Of the 17 children with reported exposure to gadolinium-based contrast agents, 7 received gadodiamide only, 2 received both gadodiamide and gadopentetate dimeglumine, 3 were exposed to multiple gadolinium-based agents (gadodiamide, gadoversetamide, gadoteridol, gadobenate dimeglumine and gadopentetate dimeglumine) and 5 had exposure to an unspecified gadolinium-based contrast agent (Fig. 1). Thus, 12 of 17 (71%) children with reported product-specific exposure to gadolinium-based contrast agents had received the linear nonionic agent gadodiamide.

Among known renal disease, 6 children reported had chronic kidney disease and only 2 had acute kidney injury. Ten were individuals on dialysis. Of the 10 children with known outcome, 5 had died and 5 had improvement of nephrogenic systemic fibrosis after kidney transplant or treatment. Characteristics for each case are shown in Table 1.

Discussion

Although 1,515 cases were reported in FAERS only 16 were 18 years or younger. The ICNSFR registry contains 384 people with biopsy-proven nephrogenic systemic fibrosis, of whom only 12 are pediatric. Moreover, of 1,280 cases in the literature of nephrogenic systemic fibrosis associated with gadolinium-based contrast agents, only 12 are identified as pediatric. In addition, in a publicly available legal data set, only one pediatric case has been reported among the 382 individual biopsy-proven, product-specific cases of nephrogenic systemic fibrosis [29]. These findings suggest that reports of nephrogenic systemic fibrosis are far less common in children than in adults. Privacy regulations severely impair the ability to identify individual cases in publicly available data sets, yet this report demonstrates how data mining of multiple publicly available sources can achieve more complete and accurate data than with any one of the data sets utilized for this study. All three data sources were utilized to cross-compare and eliminate redundant case reports.

FAERS reports were presented as scanned and redacted MedWatch forms with narratives. These reports were product-specific, each with a unique Individual Safety Report number. Manufacturers assign each report with a manufacturers' control number. While the MedWatch form allows for input of pertinent data, some forms were missing relevant details such as birth date, dose and event date. Four FAERS reports contained case-related citations allowing for reconciliation with published reports; this linkage served to confirm product-specific exposure to gadolinium-base contrast agents.

The FAERS has no clinical validation process nor does it screen for duplicates prior to entry into the database. The aim is to capture all cases through mandatory product-specific adverse event reporting by manufacturers and voluntary reporting by others. Because nephrogenic systemic fibrosis is associated with exposure to gadolinium-based contrast agents, prior exposure to these agents was usually the impetus for reporting. Theoretically, if there was uncertainty as to which agent was culpable, a case may have been reported voluntarily to more than one gadolinium-agent-producing pharmaceutical company. Then each of the companies would have reported the case to the FAERS. Hence, exposure to a

single gadolinium-based contrast agent could have generated redundant reports with unique Individual Safety Reports. Both mandatory and voluntary reporting of cases can occur. Attorneys, healthcare workers, patients and their family members are among those who can voluntarily report to FAERS, again potentially triggering duplicate reporting.

Publications offer the most clinical detail, including the progression of events leading up to the diagnosis such as the reason for imaging, the initial symptoms and signs, and therapies used. Such details, including medical history, known comorbidities, the place of care, and specialties of the treating physicians, helped facilitate the determination of non-redundant cases.

The availability of histopathology related to all 9 non-redundant literature reports helped to confirm the diagnosis. Clearly, in case reports published prior to the recognition of an association between gadolinium and nephrogenic systemic fibrosis, exposure to gadolinium-based contrast agents was not described. These missing data were obtained either by direct contact with the author or by reconciliation with the narrative information in the relevant FAERS report. As a result, this review confirmed that gadodiamide was used in all nine children in whom use of a specific gadolinium-based contrast agent was identified. This is similar to the findings in adults [23, 30, 31].

According to a 2010 FDA directive, gadodiamide (Omniscan™; GE Healthcare, Princeton, NJ), gadopentetate dimeglumine (Magnevist™; Bayer Schering Pharma, Berlin-Wedding, Germany) and gadoversetamide (Optimark™; Mallinckrodt Inc., Hazelwood, MO) are contraindicated in patients with acute kidney insufficiency or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m²) [32]. Both gadodiamide and gadoversetamide are linear, nonionic agents and gadopentetate dimeglumine is a linear, ionic agent. All three have low kinetic stability relative to other gadolinium-based contrast agents [33]. Although the pathogenesis of nephrogenic systemic fibrosis and the mechanism by which gadolinium might promote the disease remain unknown, it has been hypothesized that an agent with low stability could readily allow a gadolinium ion to detach from its chelating ligand, and this process could be more significant when elimination is delayed by poor renal function [34].

Because there are no evidence-based guidelines for the prevention of nephrogenic systemic fibrosis in children, the American College of Radiology guidelines do not indicate that children are at any different risk for nephrogenic systemic fibrosis from adults and advise that adult guidelines for dosing and administration of gadolinium-based contrast agents be followed in children with renal dysfunction [35]. Such recommendations indicate that people with severe chronic kidney disease (eGFR <30 mL/min/1.73m²) or acute kidney insufficiency avoid exposure to gadolinium-based contrast agents. Moreover if a gadolinium-based contrast agent is needed the recommendation is to use the lowest possible dose. In addition, although nephrogenic systemic fibrosis has not been reported in a child 8 years or younger, caution should be used when administering these contrast agents to neonates and infants because of renal immaturity and potential glomerular filtration rates under 30 mL/min/1.73 m² [35].

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP), based on expert opinion, recommends that high-risk gadolinium-based contrast agents (gadodiamide, gadoversetamide and gadopentetate dimeglumine) not be used in neonates younger than 4 weeks or in those with immature kidneys; the dose should also be restricted in infants younger than a year old, and 7 days should elapse before administration of an additional dose. For the other agents, CHMP recommends that the dose be restricted in neonates and infants up to 1 year of age and, similarly, that 7 days should elapse before

administration of another dose [36]. Pediatric clinicians must weigh the risks and benefits related to gadolinium-based contrast exposure before performing MR examinations with contrast agents.

Regarding the six children with no documentation of gadolinium-based contrast exposure, the International Center for Nephrogenic Systemic Research (ICNSFR) contributed these six cases. The ICNSFR makes the diagnosis of nephrogenic systemic fibrosis based upon the clinical and pathological definition published by Girardi et al. [27]. The definition of nephrogenic systemic fibrosis does not require exposure to a gadolinium-based contrast agent to reach a definitive diagnosis. Consequently, we have made no assumption about prior exposure to these agents in these six children, although the bulk of evidence from many studies suggests such an exposure almost certainly occurred. We justify inclusion of these children not because exposure can or cannot be documented, but rather to reach the most complete accounting of children with nephrogenic systemic fibrosis.

Limitations of this study include the involuntary nature of reporting to FAERS that renders many reports incomplete, despite product-specific information. The issues of redundancy, voluntarism and redaction also provide significant challenges to accurate data authentication. Although only children 18 years or younger were identified, pediatric nephrology centers often follow patients to age 21.

Conclusion

This study reflects a collaborative effort to verify reporting of nephrogenic systemic fibrosis in children. Because this entity is so rare it is important to minimize the effect of over-reporting and redundancy and to confirm that each case is unique. By reviewing published literature as well as the FAERS and the ICNSFR registry databases, we have determined that nephrogenic systemic fibrosis in children is rare.

Acknowledgments

This project was supported by NIH grants 2 R01 CA102713-03A2 (DPW), 1 R01 CA125077-01A1 (DPW) and 1 K01 CA134554-01 (JMM).

References

1. Cowper SE, Robin HS, Steinberg SM, et al. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. *Lancet*. 2000; 356:1000–1001. [PubMed: 11041404]
2. Ting WW, Stone MS, Madison KC, et al. Nephrogenic fibrosing dermatopathy with systemic involvement. *Arch Dermatol*. 2003; 139:903–906. [PubMed: 12873886]
3. Cowper SE, Bucala R, Leboit PE. Nephrogenic fibrosing dermatopathy/nephrogenic systemic fibrosis -- setting the record straight. *Sem Arthritis Rheum*. 2006; 35:208–210.
4. Galan A, Cowper SE, Bucala R. Nephrogenic systemic fibrosis (nephrogenic fibrosing dermatopathy). *Curr Opin Rheumatol*. 2006; 18:614–617. [PubMed: 17053507]
5. Auron A, Shao L, Warady BA. Nephrogenic fibrosing dermatopathy in children. *Pediatr Nephrol*. 2006; 21:1307–1311. [PubMed: 16821025]
6. Prince MR, Zhang HL, Prowda JC, et al. Nephrogenic systemic fibrosis and its impact on abdominal imaging. *Radiographics*. 2009; 29:1565–1574. [PubMed: 19959508]
7. Morcos SK. Nephrogenic systemic fibrosis following the administration of extracellular gadolinium based contrast agents: is the stability of the contrast agent molecule an important factor in the pathogenesis of this condition? *Br J Radiol*. 2007; 80:73–76. [PubMed: 17392401]
8. Dillman JR, Ellis JH, Cohan RH, et al. Frequency and severity of acute allergic-like reactions to gadolinium-containing i.v. contrast media in children and adults. *AJR Am J Roentgenol*. 2007; 189:1533–1538. [PubMed: 18029897]

9. Halvorsen RA. Which study when? Iodinated contrast-enhanced CT versus gadolinium-enhanced MR imaging. *Radiology*. 2008; 249:9–15. [PubMed: 18796664]
10. Martin DR. Nephrogenic systemic fibrosis. *Pediatr Radiol*. 2008; 38(Suppl1):S125–129. [PubMed: 18071694]
11. Saab G, Abu-Alfa A. Nephrogenic systemic fibrosis -- implications for nephrologists. *Eur J Radiol*. 2008; 66:208–212. [PubMed: 18342470]
12. Joffe P, Thomsen HS, Meusel M. Pharmacokinetics of gadodiamide injection in patients with severe renal insufficiency and patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis. *Acad Radiol*. 1998; 5:491–502. [PubMed: 9653466]
13. Abu-Alfa AK. Nephrogenic systemic fibrosis and gadolinium-based contrast agents. *Adv Chronic Kidney Dis*. 2011; 18:188–198. [PubMed: 21531325]
14. Grobner T, Prischl FC. Patient characteristics and risk factors for nephrogenic systemic fibrosis following gadolinium exposure. *Semin Dial*. 2008; 21:135–139. [PubMed: 18226001]
15. Dharnidharka VR, Wesson SK, Fennell RS. Gadolinium and nephrogenic fibrosing dermatopathy in pediatric patients. *Pediatr Nephrol*. 2007; 22:1395. [PubMed: 17180360]
16. DiCarlo JB, Gupta EA, Solomon AR. A pediatric case of nephrogenic fibrosing dermatopathy: improvement after combination therapy. *J Am Acad Dermatol*. 2006; 54:914–916. [PubMed: 16635686]
17. Foss C, Smith JK, Ortiz L, et al. Gadolinium-associated nephrogenic systemic fibrosis in a 9-year-old boy. *Pediatr Dermatol*. 2009; 26:579–582. [PubMed: 19840315]
18. Jain SM, Wesson S, Hassanein A, et al. Nephrogenic fibrosing dermatopathy in pediatric patients. *Pediatr Nephrol*. 2004; 19:467–470. [PubMed: 14872332]
19. Jan F, Segal JM, Dyer J, et al. Nephrogenic fibrosing dermatopathy: two pediatric cases. *J Pediatr*. 2003; 143:678–681. [PubMed: 14615747]
20. Krous HF, Breisch E, Chadwick AE, et al. Nephrogenic systemic fibrosis with multiorgan involvement in a teenage male after lymphoma, Ewing's sarcoma, end-stage renal disease, and hemodialysis. *Pediatr Dev Pathol*. 2007; 10:395–402. [PubMed: 17929984]
21. Sanchez-Ross M, Snyder R, Colome-Grimmer MI, et al. Nephrogenic fibrosing dermatopathy in a patient with systemic lupus erythematosus and acute lupus nephritis. *Pediatr Dermatol*. 2007; 24:E36–39. [PubMed: 17958777]
22. Sharma J, Mongia A, Schoenaman M, et al. Nephrogenic fibrosing dermatopathy, cardiac calcification and pulmonary hypertension in an adolescent on chronic hemodialysis. *Indian J Nephrol*. 2008; 18:70–73. [PubMed: 20142906]
23. Wiginton CD, Kelly B, Oto A, et al. Gadolinium-based contrast exposure, nephrogenic systemic fibrosis, and gadolinium detection in tissue. *AJR AmJ Roentgenol*. 2008; 190:1060–1068. [PubMed: 18356456]
24. McKoy JM, Fisher MJ, Courtney DM, et al. Results from the first decade of research conducted by the Research on Adverse Drug Events and Reports (RADAR) Project. *Drug Saf*. 2013; 36:335–347. [PubMed: 23553448]
25. Bennett CL, Nebeker JR, Lyons EA, et al. The Research on Adverse Drug Events and Reports (RADAR) project. *JAMA*. 2005; 293:2131–2140. [PubMed: 15870417]
26. Cowper, S. [Accessed Dec. 14, 2011] Nephrogenic systemic fibrosis (ICNSFR Website). 2011. Retrieved from <http://www.icnsfr.org>
27. Girardi M, Kay J, Elston DM, et al. Nephrogenic systemic fibrosis: clinicopathological definition and workup recommendations. *J Am Acad Dermatol*. 2011; 65:1095–1106. [PubMed: 21724294]
28. Matsumoto Y, Mitsuhashi Y, Monma F, et al. Nephrogenic systemic fibrosis: a case report and review on Japanese patients. *J Dermatol*. 2012; 39:449–453. [PubMed: 22035371]
29. Nardone B, Laumann AE, Edwards BJ, et al. Advancing pharmacovigilance through analysis of gadolinium-based contrast agent (GBCA) exposure dataset for nephrogenic systemic fibrosis -- a RADAR report. *J Am Acad Dermatol*. 2012; 66(Suppl 1):AB5.
30. Bongartz G. Imaging in the time of NFD/NSF: do we have to change our routines concerning renal insufficiency? *MAGMA*. 2007; 20:57–62. [PubMed: 17436028]

31. Kanal E, Barkovich AJ, Bell C, et al. ACR guidance document for safe MR practices: 2007. *AJR Am J Roentgenol.* 2007; 188:1447–1474. [PubMed: 17515363]
32. U.S. Food and Drug Administration. [Accessed March 17, 2011] FDA Drug Safety Communication: New warnings for using gadolinium-based contrast agents in patients with kidney dysfunction. 2010. Retrieved from <http://www.fda.gov/Drugs/DrugSafety/ucm223966.htm>
33. Morcos SK, Haylor J. Pathophysiology of nephrogenic systemic fibrosis: a review of experimental data. *World J Radiol.* 2010; 2:427–433. [PubMed: 21179310]
34. Grobner T. Gadolinium -- a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant.* 2006; 21:1104–1108. [PubMed: 16431890]
35. ACR Committee on Drugs and Contrast Media. [Accessed June 3, 2013] ACR manual on contrast media. 2013. Retrieved from http://www.acr.org/~media/ACR/Documents/PDF/QualitySafety/Resources/Contrast%20Manual/2013_Contrast_Media.pdf
36. European Medicines Agency. [Accessed September 18, 2011] Questions and answers on the review of gadolinium-containing contrast agents. 2010. Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_31/WC500015635.pdf
37. Araya, CE.; Dharnidharka, VR. Use of contrast agents in children with chronic kidney disease. In: Warady, BA.; Schaefer, F.; Alexander, SR., editors. *Pediatric dialysis.* Springer; New York: 2011. p. 629-644.

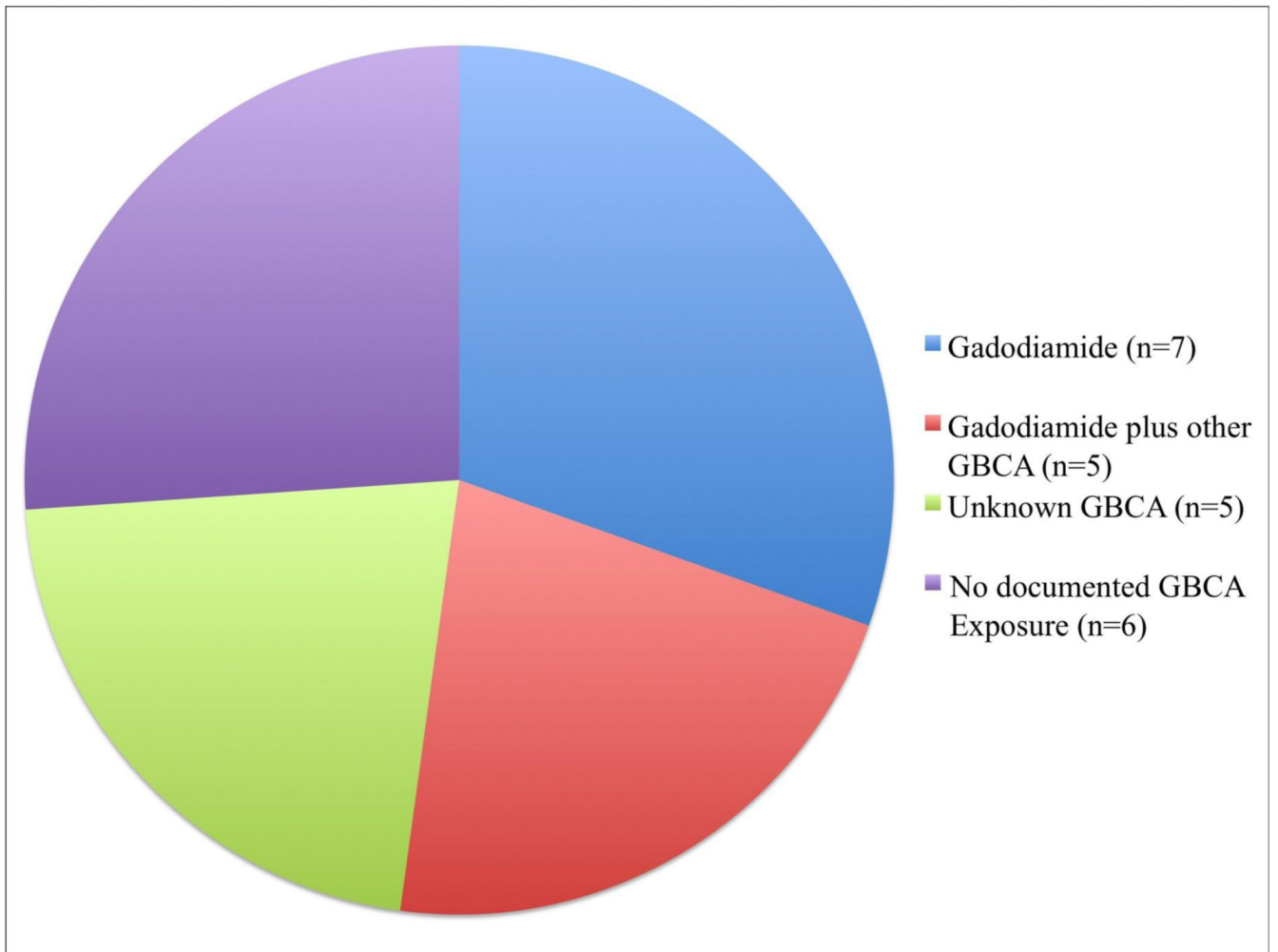


Fig. 1. Reported and unreported exposure to gadolinium-based contrast agents in 23 children with nephrogenic systemic fibrosis. *GBCA* gadolinium-based contrast agent

Table 1

Reported exposure to gadolinium-based contrast agents and outcome for 23 children with nephrogenic systemic fibrosis [37]

Case number	Age(yrs)/gender/race	Renal disease/dialysis	GBCA	Cumulative dose	Outcome	Source/report date
1	6/NA/NA	NA	NA	NA	NA	ICNSFR January 2004
2	8/male/NA	CKD	Gadodiamide	Single dose	Skin improvement after kidney transplant	ICNSFR, FAERS February 2000
3	9/male/Caucasian	PD	Gadodiamide	Single dose	Deceased Cardiac arrest Pulmonary embolus	Jain et al. [18] (2004) Dharmidharka et al. [15] (2006) FAERS, ICNSFR
4	9/male/NA	AKI, PD, HD	Gadodiamide	0.1 + 0.3 mmol/kg	NA	Foss et al. [17] (2009) FAERS
5	11/male/NA	CKD, HD	Gadoversetamide Gadoteridol, Gadobenic acid Gadodiamide Gadopentetate dimeglumine	> 50 mL	Deceased after kidney transplant. Cardiac arrest	Krous et al. [20] (2007) FAERS, ICNSFR June 2004
6	11/male/NA	NA	Gadopentetate dimeglumine Gadodiamide Gadoversetamide Gadobenate Dimeglumine Gadoteridol	NA	Deceased Cardiac arrest	FAERS September 2011
7	13/male/Caucasian	ESRD PD	Unknown GBCA (per author follow-up)	NA	Deceased	Aaron et al. [5] (2006) Jan et al. [19] (2003)
8	13/NA/NA	NA	Gadodiamide	Single dose	NA	FAERS January 2007
9	14/NA/NA	Renal Osteodystrophy	NA	NA	NA	ICNSFR October 2004
10	14/female/NA	AKI, HD	Gadodiamide	0.26 mmol/kg	Decrease in areas of induration and number and size of papular lesions; decrease in discomfort after 6	Sanchez-Ross et al. [21] (2007) Wiginton et

Case number	Age(yrs)/gender/race	Renal disease/dialysis	GBCA	Cumulative dose	Outcome	Source/report date
11	14/male/Hispanic	PD, HD	Unknown GBCA	Single dose	months of hydroxychloroquine therapy. No response to the treatment (unknown). Deceased 2 years later. Cardiac arrest	al. (2008 [23] FAERS Sharma et al. [22] (2008)
12	14/male/NA	PD	Gadodiamide Gadopenetate dimeglumine	40 mL	NA	FAERS January 2008
13	14/male/Asian	CKD secondary to hydronephrosis resulting from an ureterocele/ PD	Gadopenetate dimeglumine Gadodiamide	40mL	Skin hardening and keratotic papules of his extremities resolved (at 2-year follow-up)	FAERS Matsumoto et al. [28] (2012)
14	15/NA/NA	NA	Unknown GBCA	NA	NA	ICNSFR July 2005
15	16/female/Caucasian	CKD, PD, HD	Unknown GBCA (per author follow-up)	NA	Improvement with softening of the skin lesions and no new areas after kidney transplant which was done 2 years after NSF diagnosis and 15 months after starting PD. Later rejected transplant. Deceased on Nov 2008.	Jan et al. [19] (2003)
16	16/male/NA	NA	Gadopenetate dimeglumine Gadodiamide Gadoversetamide Gadobenate dimeglumine Gadoteridol	NA	NA	FAERS June 2011
17	16/NA/NA	NA	NA	NA	NA	ICNSFR
18	17/male/NA	PD	Gadodiamide	20 mL	Near-complete resolution after treatment with triamcinolone 0.1% and calcipotriene 0.005% + compression stockings/nocturnal leg elevation. Additional benefit with 3days of pulsed IV methylprednisolone 750 mg followed by weekly methotrexate	DiCarlo et al. [16] (2006) FAERS, ICNSFR
19	17/NA/NA	NA	Unknown GBCA	NA	NA	ICNSFR March 2005

Case number	Age(yrs)/gender/race	Renal disease/dialysis	GBCA	Cumulative dose	Outcome	Source/report date
20	17/NA/NA	NA	NA	NA	NA	ICNSFR June 2006
21	18/NA/NA	NA	NA	NA	NA	ICNSFR July 1997
22	18/NA/NA	NA	NA	NA	NA	ICNSFR March 2004
23	<18/female/NA	ESRD	Gadodiamide	Single dose	NA	FAERS September 2008

AKI acute kidney injury, CKD chronic kidney disease, ESRD end-stage renal disease, FAERS U.S. Food and Drug Administration Adverse Event Reporting System, GBCA gadolinium-based contrast agent, HD hemodialysis, ICNSFR International Center for Nephrogenic Systemic Fibrosis Research, NA not available, PD peritoneal dialysis, IV intravenous