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EDUCATIONAL REVIEW

Gadolinium and nephrogenic systemic fibrosis: an update

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Abstract Nephrogenic systemic fibrosis (NSF) is a multisystem disease seen exclusively in patients with renal impairment. It can be severely debilitating and sometimes fatal. There is a strong association with gadolinium-based contrast agents used in magnetic resonance imaging (MRI). Risk factors include renal impairment and proinflammatory conditions, e.g. major surgery and vascular events. Although there is no single effective treatment for NSF, the most successful outcomes are seen following restoration of renal function, either following recovery from acute kidney injury or following renal transplantation. There have been ten biopsy-proved pediatric cases of NSF, with no convincing evidence that children have a significantly altered risk compared with the adult population. After implementation of guidelines restricting the use of gadolinium-based contrast agents in at-risk patients, there has been a sharp reduction in new cases and no new reports in children. Continued vigilance is recommended: screening for renal impairment, use of more stable gadolinium chelates, consideration of non-contrast-enhanced MRI or alternative imaging modalities where appropriate.

Keywords Nephrogenic systemic fibrosis · Nephrogenic fibrosing dermopathy · Magnetic resonance imaging · Gadolinium · Contrast agents · Kidney disease · End-stage renal disease · Children

Introduction

Nephrogenic systemic fibrosis (NSF) is a multisystem fibrosing condition observed in patients with renal impairment [1]. It causes morbidity through systemic fibrosis, including skin fibrosis and associated joint contractures. The occurrence of NSF following gadolinium (Gd)-based contrast-agent administration was first reported in 2006 [2]. These agents are used in magnetic resonance imaging (MRI) to improve diagnostic efficacy. Their use is widespread, with millions of examinations performed annually. NSF has been reported in approximately 500 patients worldwide, but in dialysis patients given high doses of Gd, the incidence is as high as 18 % [3]. Only ten biopsy-proven cases in children have been reported [4]. We will discuss the emergence of NSF as a clinical entity and consider the evidence for Gd as a causative agent. This includes a review of the impact of international guidelines restricting the use of Gd on the incidence of NSF since 2006 and an overview of alternative and adapted imaging techniques available for children with renal impairment.

NSF as a distinct clinicopathological entity

Cowper et al., in 2000, were the first authors to describe nephrogenic fibrosing dermopathy as a distinct clinical entity in a series of 15 patients [1]. These cases had either received or were receiving renal dialysis and presented with thickening and hardening of the skin with brawny hyperpigmentation in a typically symmetrical distribution, most commonly affecting the extremities from ankles to midthighs and from wrists to midupper arms. Deep-skin biopsy showed extensive fibrosis that was different histologically from clinically similar entities.

The term nephrogenic systemic fibrosis (NSF) emerged following reports of systemic involvement seen at autopsy, including a report of respiratory failure following extensive phrenic fibrosis [5, 6]. Myopathy and polyneuropathy have also been demonstrated [7]. However, due to the high level of comorbidity in this patient group, there may be some overlap with systemic fibrosis due to other causes, such as uremic cardiomyopathy or uremic pleurisy [8, 9]. NSF has no single diagnostic, clinical or histologic feature. The clinical picture in NSF is very similar to scleromyxedema, but NSF favors the extremities and trunk

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rather than the head and neck [10]. Other differentials such as morphea differ both clinically and histologically) [11]. Deep-skin biopsy that includes the fascia is essential for diagnosis. Early histological descriptions were of dermal spindle-cell proliferation and disorganized, thickened collagen bundles separated by clefts and with variable quantities of mucin and elastic fibers. Differentiating features from similar clinical entities includes dual positivity of fibrocytes for CD34 and procollagen 1, although this can be seen in other fibrosing lesions such as scleroderma [12]. Additionally, rather than deriving from dermal dendrocytes, the dominant cell in dermal biopsies in NSF has a similar immunohistochemical fingerprint to bone-marrow-derived circulating fibrocytes [13]. Osseous metaplasia with disorganized fragments of bone may also be seen on skin biopsy in NSF. This finding appears to be relatively specific, although its significance is unclear [14] Following are differential diagnoses for NSF in adults and children:

- Scleromyxedema
- Lipodermatosclerosis
- Eosinophilia-myalgia syndrome
- Eosinophilic fasciitis (Schulman syndrome)
- Systemic sclerosis/morphea
- Porphyria cutanea tarda
- Fibroblastic rheumatism
- Scleredema
- $\beta_2$microglobulin amyloidosis
- Dermatofibrosarcoma protuberans

The International Center for Nephrogenic Systemic Fibrosis Research (ICNSFR) is a collaborative research group based at Yale University, New Haven, CT, USA. A component of this is the NSF Registry, a database of biopsy-confirmed cases of NSF. In 2009 the organization proposed a clinicopathological scoring system derived from published literature and registry data aimed at achieving diagnostic standardization (Tables 1, 2 and 3 and Fig. 1) [15].

How serious a problem is NSF?

More than 500 cases of NSF have been reported to MedWatch, the US Food and Drugs Administration (FDA) database [16]. However, as MedWatch does not require histopathological confirmation, this is likely an overestimate. The NSF Registry at Yale holds a little more than 360 cases, and a recent review counted 408 biopsy-confirmed cases of NSF in the literature [18]. Confirmed cases of NSF have been reported in patients from 8 years to 87 years old, with a peak incidence at ages 51–60 years. There is no significant gender or racial predilection.

The natural history of NSF is variable [19]. As the condition progresses, the skin may take on a woody texture. Joint contractures or reduced range of movement are seen in >60 % of patients [18]. Of 345 patients in the NSF Registry in 2009, almost 10 % were known to be restricted to a wheelchair (ICNSFR http://www.icnsfr.org). It is estimated that 5 % of patients have a rapidly progressive course, and NSF may increase mortality rates through restricted mobility and, more rarely, restricted ventilation [6]. However, there is a high level of background morbidity, and no controlled trials have explored mortality directly attributable to NSF. One study of non-biopsy-proven cases suggested a 48 % mortality rate over 48 months in patients with features of NSF compared with 20 % in hemodialysis patients without cutaneous disease [20].

Table 1 Proposed criteria for the diagnosis of nephrogenic systemic fibrosis (NSF): clinical features

Major clinical criteria	Minor clinical criteria
Patterned plaques	Puckering/linear banding
Joint contractures	Superficial NSF (plaque/patch)
Cobblestoning	Dermal papules
Marked induration/peau d'orange	Scleral Plaques (pt <45yo)

Table 2 Proposed histological criteria for the diagnosis of nephrogenic systemic fibrosis (NSF), for which deep excisional dermal biopsy including fascia is essential [14]

1) Increased Cellularity (spindle/epitheliod) with few other inflammatory cells
2) CD34+ spindle or epetheliod cells in reticular or tram-track arrangement
3) Both fine collagen and ropey collagen surrounded by clefts
4) Elastic fibers preserved (score -1 if elastic fibers absent)
5) Septal involvement
6) Osseous metaplasia (score +3)

Evidence for a link with gadolinium-based contrast agents

Gd-based contrast agents exploit the paramagnetic nature of the Gd^{3+} cation (bound to a chelating agent in clinical

Table 3 Proposed combined clinical and histological scoring system for the diagnosis of nephrogenic systemic fibrosis (NSF)

Clinical score	Histological score
4=Consistent with NSF (> 1 major criteria)	4=Consistent with NSF (4 or 5 criteria)
3=Suggestive of NSF (1 major criteria)	3=Suggestive of NSF (3 criteria)
2=Inconsistent with NSF (>1 minor criteria)	2=Inconsistent with NSF (2 criteria)
1=NSF ruled out (0–1 minor criteria)	1=NSF ruled out (1 criteria)
0=Diagnostic of an entity other than NSF	0=Another diagnosis can be made

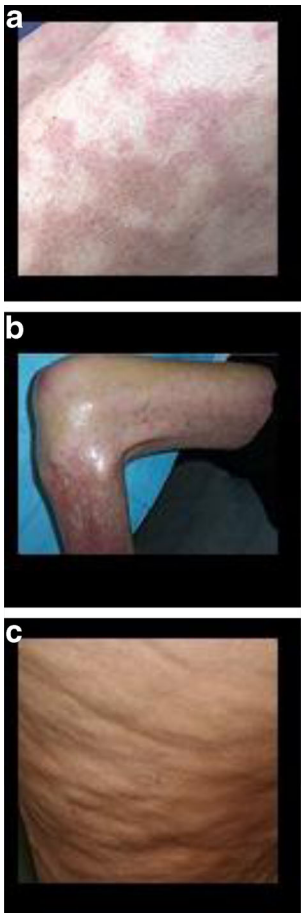

Fig. 1 **a** Hyperpigmented brawny-patterned plaques (major criterion). Red to violaceous thin, fixed plaques showing polygonal, reticular, or amoeboid morphologies (with permission from [15]). **b** Joint contractures (major criterion): end-stage NSF with fixed contracture of the knee (reprinted with permission [17]. **c** Cobblestoning (major criterion): This bumpy pattern resembles rounded paving stones (reprinted with permission [17]

preparations), increasing the relaxation rate and thereby the MRI signal on T1-weighted sequences [21]. The main uses are: (1) highlighting inflammation and neoplasia, and (2) in magnetic resonance angiography (MRA). Nonenhanced MRA is now commonly available, but there remains a large group of patients across a range of specialties in whom Gd-based contrast agents provide added diagnostic information.

The factor common to all patients with NSF is renal impairment, in particular, end-stage kidney disease. Before 2006, risk factors identified from individual case reports and small retrospective series failed to identify a single agent that came close to satisfying the Hill criteria for causality [22]. NSF was frequently reported immediately following proinflammatory events or in hypercoagulable states, with preceding surgery in up to 90 % of cases [11]. Erythropoietin use was seen in up to 80 %, although this may simply have reflected erythropoietin resistance relating to chronic inflammation [23]. Other risk factors, including liver disease [24], immunosuppression [25], hyperphosphatemia [26], and acidosis [2], were reported but not consistently reproduced. At this stage, it appeared that NSF involved a process of sensitizing events (renal disease and some proinflammatory condition) and an unidentified trigger (e.g., allergen deposition) [27].

In 2006, Groebner reported a series of five patients with end-stage kidney disease who developed NSF 2–4 weeks following Gd-enhanced MRA [2]. This association with Gd sparked immediate research into its possible role in NSF, and case series and retrospective case–control analyses have subsequently reported Gd-based contrast administration prior to NSF onset in nearly all cases [26, 28] (Table 4).

The reported delay between Gd exposure and NSF presentation varies greatly for individual patients, ranging from a few days to 3 years, with a median of 62 days [18]. The incidence of NSF following Gd administration in renally impaired patients varies between 0 % and 18 %. The highest incidence has been seen in perioperative renal transplant patients on maintenance peritoneal dialysis undergoing high-dose MRA [3]. A 2008 meta-analysis of 4,276 patients with renal impairment found strong and consistent increased risk of developing NSF for patients exposed to Gd compared with those not exposed [odds ratio (OR) 26.7, 95 % confidence interval (CI) 10.3–69.4] [41].

Several reports suggest a dose–response relationship, and it is interesting to note that the first known cases of NSF, which occurred in 1997, followed a 1993 FDA approval of double- and triple-dose gadodiamide MRA [31]. Data on the type and dose of Gd used is not available in all studies. For those studies that do report dose–effect, an increased NSF risk with either increasing cumulative Gd dose over multiple examinations or with a high single dose during a single examination is recorded [30, 33, 36, 42–44]. One observational study reports an average 2.4 % risk of developing NSF for each radiological study using Gd in at-risk patients [32].

Boyd et al. were the first to detect Gd in NSF-related skin lesions in 2007 [45]. Their findings were subsequently reproduced—including at autopsy where extracellular Gd was found in multiple organs in patients with NSF. Gd deposits are rarely seen in exposed patients who have not developed NSF, and no deposits have been found in nonexposed patients [46]. It is postulated that Gd dissociation leads to insoluble Gd salt deposition in the interstitium, providing a nidus for fibrosis [47]. Free Gd has indeed been shown to stimulate human fibroblast proliferation in vitro, with hyaluronan and collagen synthesis, as seen in biopsies from patients with NSF [48]. Although the majority of the in vitro studies relate to nonchelated Gd as a trigger for NSF, human macrophages and monocytes also express pro-fibrotic cytokines and growth factors capable of stimulating NSF-like fibrosis in response to chelated gadodiamide and gadopentetate dimeglumine [49]. Several NSF-patients in whom no Gd exposure could be ascertained have been reported [33, 50]. These include patients with solid-organ transplants, one of whom had positive lupus anticoagulant, and one with confirmed vascular thrombosis and hepatitis C.

In summary, for approximately 90 % of cases, there is a clear temporal sequence between Gd administration and NSF

Table 4 Risk of nephrogenic systemic fibrosis (NSF) in patients with renal impairment exposed to gadolinium (Gd)-based contrast agents. This includes odds ratio (where available) for developing NSF following exposure

	Patients exposed to Gd	No. of NSF cases	Risk of NSF after Gd exposure	Odds ratio for developing NSF
Marckmann [29]	370 CKD 5	13	3.5 %	32.5
Kallen [30]	Case–control, patients on dialysis and with AKI	19 cases, 57 controls	0.6 % (HD) 4.6 % (PD)	8.97
Broome [31]	301 dialysis	12	4.0 %	22.3
Deo [32]	87 dialysis	3	3.4 % 2.4 % risk for each Gd exposure	31.5
Collidge [33]	421 dialysis	14	3.1 %	
Othersen [28]	261 dialysis	4	1.5 %	6.67 for single exposure 44.5 for multiple exposures
Wiginton [34]	72 dialysis	2	2.8 %	0.82 (95% CI 0.04–18.10)
Prince [35]	265 CKD 5 120 AKI	1 11	0.4 % 9.2 %	
Sadowski [36]	393 CKD 3–5	13 (6 on HD)	3.3 %	
Lauenstein [37]	312 dialysis	9	2.6 %	
Rydahl [3]	102 CKD 5	18	18 %	
Shabana [38]	414 dialysis	12	2.9 %	
Chrysochou [39]	2053 CKD 2–5	0	0 %	
Heinz-Peer [40]	367 dialysis	6	1.6 %	
Bahrami [25]	209 dialysis	4	1.9 %	

CKD chronic kidney disease; *AKI* acute kidney injury; *HD* hemodialysis; *PD* peritoneal dialysis, *CI* confidence interval

development. Data show a strong association between Gd exposure and NSF, and there is a likely dose–response relationship. This suggests a causal link. The validity of adult data extrapolated to children is unknown.

Role of different gadolinium-based contrast agents

Free Gd is toxic and may cause splenic degeneration, central lobular hepatic necrosis, competitive calcium-channel inhibition, and a variety of hematological pathologies [51]. The different classes of Gd chelates used clinically are ionic or nonionic ligand-binding groups within either linear, nonlinear, or macrocyclic molecules that trap Gd and facilitate renal—and to a lesser extent, hepatic—excretion (Table 5). Their plasma half life is around 2 h in people with normal renal function and 30 h—120 h in those with renal impairment [53].

If, as postulated, free Gd stimulates NSF, increased dissociation from chelating compounds should result in increased NSF risk. Dissociation increases with reduced clearance (renal impairment), low thermodynamic and kinetic stability of some Gd contrast agents, and acidosis. The predominant process responsible for dissociation is thought to be transmetallation with endogenous zinc ions (and to a lesser extent with copper, calcium, or iron ions). Chelates have different thermodynamic and kinetic stabilities. Although kinetic stability plays a more significant role than thermodynamic stability in vivo [54], both reduce in a similar order: macrocyclic ligands have high stability, ionic open-chain ligands moderate stability, and nonionic open-chain chelates the lowest stability [51]. In rats, administration of different contrast agents has been shown to induce NSF-like cutaneous fibrosis and Gd deposits following gadodiamide administration, but no such reaction is seen for other agents, including gadoversetamide, gadopentetate dimeglumine, gadobenate dimeglumine, gadoterate meglumine, and gadobutrol [55]. Human studies in patients with normal renal function have confirmed two- to four-times higher concentrations of Gd in bone following gadodiamide than the macrocyclic preparation gadoteridol [56].

Retrospective analysis of the role of different agents is limited, as the specific agent is often either not recorded or because any one patient may have been exposed to multiple contrast agents. A review in 2008 reported unconfounded association to be most frequent for gadodiamide, followed by gadopentetate dimeglumine. Confounded association has been reported with both linear and macrocyclic Gd contrast agents [57], as are cases of NSF after unconfounded exposure to the macrocyclic agents gadobutrol and gadoterate meglumine [58]. In reality, there is inadequate data to evaluate whether the risk of NSF varies significantly between different contrast agents due to: (1) the small total number of cases of NSF; (2) uncertainty of the specific agent used; (3) the large proportion of market share possessed by gadopentetate dimeglumine and gadodiamide in the relevant time period. Interaction between chelate stability, prolonged contrast-agent circulation, and

Table 5 Gadolinium (Gd) contrast agents, their approval status in the USA and Canada, and classification as high, medium, or low risk in Europe. In Europe, with the exception of Optimark, individual Gd agents are approved for clinical use on a national rather than central level

Brand name	Product	Excretion [52]	US FDA approval	Canadian TPD approval
High-risk (EU classification)				
Omniscan (linear chelate)	Gadodiamide Gd-DTPA-BMA	Renal	Adult CNS, body Pediatric CNS, body >2 years	Adult CNS, body, breast, MRA Pediatric CNS >2 years, CI in NN
Optimark (linear)	Gadoversetamide Gd-DTPA-BMEA	Renal	Adult CNS, liver No pediatric approval—caution <18 years	Adult CNS, liver No pediatric approval—caution <18 years, CI in NN
Magnevist (linear)	Gadopentetate dimeglumine Gd-DTPA	Renal	Adult CNS, body, head/neck. Pediatric CNS, body, head/neck >2 years.	Adult CNS, head/neck Pediatric CNS>2 year,s CI in NN
Medium risk (EU classification)				
Multihance (linear)	Gadobenate dimeglumine BOPTA	97 % renal, 3 % biliary	Adult CNS, MRA Pediatric CNS >2 years	Adult CNS, MRA Pediatric CNS >2 years
Primovist (Eovist in USA) (linear)	Gadoxetate disodium Gd-EOB-DTPA	50 % renal, 50 % biliary	Adult MRI liver Not approved <18 years	Adult MRI liver Not approved <18 years
Vasovist (Ablavar in USA and Canada) (linear)	Gadofosveset trisodium MS325	91 % renal, 9 % biliary	Adult MRA Not approved <18 years	Adult MRA Not approved <18 years
Low risk (EU classification)				
Gadovist (Gadavist in USA) (macrocyclic)	Gadobutrol Gd-BT-DO3A	Renal	Adult and pediatric CNS >2 years	Adult CNS, MRA Pediatric CNS, MRA>2 years
Prohance (macrocyclic)	Gadoteridol GD-HP-DO3A	Renal	Adult CNS, head/neck Pediatric CNS>2 years	Adult CNS, head/neck Pediatric CNS>2 years
Dotarem (macrocyclic)	Gadoterate meglumine Gd-DOTA	Renal	Adult and pediatric CNS >2 years	No listing

EU European Union, *CNS* central nervous system: brain, spine, and surrounding structures, *MRA* magnetic resonance angiography. *CI in NN* contraindicated in neonates up to 4 weeks, *FDA* Food and Drug Administration, *TPD* Canadian Therapeutic Products Directorate

tissue pH leading to Gd release therefore remains incompletely understood, as is the role of Gd in the uncontrolled proliferation of fibrocytes in NSF.

NSF risk: renal impairment and liver disease

Up to December 2010, 79 % of patients with NSF recorded in the Yale Registry were receiving renal dialysis, and 17 % were nondialyzed patients with acute kidney injury (AKI), unspecified renal insufficiency, or chronic kidney disease (CKD) stage 4 or 5. The remaining were in the immediate post-renal-transplant period [16]. Until 2011, no cases of NSF had been reported in CKD stage 3, and there were limited reports in CKD stage 4 [39, 59]. One recent study from 2011, however, reported three cases of NSF in patients with CKD stage 3 and 4 [58]. An association with liver disease has been reported, some of which are within the peritransplant period, although this is in a small number of cases, and concomitant renal impairment is present in all cases. A review of 335 NSF cases in 2009 confirmed liver disease in 41 patients but failed to demonstrate any statistically significant increased risk due to the liver disease alone. Renal impairment was severe in all cases bar one, in which AKI was described [24]. The conclusion drawn in the European and American guidelines is that patients most at risk of NSF are those with CKD stage 4 or 5, including those needing dialysis and those with reduced renal function who have or are awaiting liver transplantation. Patients with CKD stage 3 (glomerular filtration rate 30–59 ml/min) and children <1 year of age are considered to have moderately increased risk [60].

Published guidelines

In May 2006, the Danish Medicines Agency reported 25 cases of NSF in Europe among patients with recent gadodiamide exposure. One month later, the US FDA advised that Gd contrast be used only if clearly necessary in patients with CKD stage 4–5 [60]. The approval status of commonly available Gd preparations in different jurisdictions is summarized in Tables 5 and 6.

Table 6 Summary of the 2010 European Medicines Agency guidelines (www.ema.europa.eu). Gadolinium-based contrast agents (GBCA) are risk stratified as shown in Table 5

Patients at risk	Risk stratification
Patients with severely impaired renal function	High-risk GBCAs: Contra-indicated Medium- and low-risk GBCAs: use lowest possible dose, pause of 7 days between two GBCA enhanced procedures
Patients with moderately impaired renal function	High-risk GBCAs: Use single injection of minimum dose, pause 7 days between two GBCA enhanced procedures Medium- and low-risk GBCAs: Use minimum dose, pause 7 days between two GBCA enhanced procedures
Infants<1 year	High-, medium-, and low-risk GBCAs: Use single injection of minimum dose, pause 7 days between two GBCA enhanced procedures
Neonates<4 weeks	High-risk GBCAs: Contraindicated Medium- and low-risk GBCAs: Use lowest possible minimum dose, pause 7 days between two GBCA enhanced procedures
Breast-feeding mothers	High-risk GBCAs: Pause for 24 h Medium- and low-risk GBCAs: Consider pause for 24 h
Perioperative phase of liver transplantation	High-risk GBCAs: Contraindicated Medium and low risk GBCAs: Use lowest possible minimum dose, pause 7 days between two GBCA enhanced procedures

In 2007, US FDA (http://www.FDA.gov) and European Society of Urogenital Radiology (ESUR) (http://www.esur.org) guidelines warned of the increased risk in acute or chronic severe renal insufficiency, hepatorenal syndrome, and the perioperative liver transplantation period. The European Medicines Agency (EMA) (http://www.ema.europa.eu) guidelines named gadodiamide, gadopentetate dimeglumine, and gadoversetamide as high risk and as being contraindicated in patients with GFR<30 ml/min/m^2. They also advised caution in patients with CKD stage 3 or in children <1 year old (Table 6). In 2009, the EMA's recommended that high-risk Gd-based contrast agents are avoided in neonates, and the minimum dose is used in infants up to 1 year old and with CKD stage 3. For medium- and low-risk Gd agents, minimum dose was recommended in, among other groups, neonates and infants up to 1 year [61]. The 2010 FDA guidelines contraindicate high-risk Gd contrast agents in patients with AKI or CKD stage 4–5 [60]. The FDA also suggests prompt hemodialysis following Gd for those already on hemodialysis, although this practice is not encouraged by the EMA.

Taking sales figures as a surrogate for quantities of Gd prescribed, there has been a decrease in worldwide sales of gadodiamide (the agent most frequently associated with NSF) since 2007 against a backdrop of increasing sales prior to this period (Evaluate Pharma, London, UK, 2012; http://www.evaluategroup.com). This is despite an increase in the overall number of MRI scans performed after 2007 (Food and Drugs Administration Joint Meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committees, December 2009; http://www.FDA.gov). This reflects a culture shift highlighted by a recent report of widely adopted policy changes among nephrologists across the USA relating to Gd contrast use in renal impairment and awareness of the risk factors and morbidity associated with NSF[62]. Since 2007, there has been a dramatic drop in the number of NSF cases reported, with multiple large studies in Sweden and the USA identifying reduced incidence or no new cases of NSF following restrictive prescribing policies [42, 44, 59, 63]. In particular, no new pediatric cases of NSF have been reported to the Yale Registry in the period 2007–2013 (personal communication, Yale NSF Registry). These results are promising and imply that NSF is unlikely to occur if guidelines limiting Gd-based contrast administration are followed. However, in 2009, well after introduction of guidelines, there was a wide variation in practice across institutions in the UK, where some departments were not adhering to European guidelines [64].

Treatment and prevention

Gd administration is sometimes essential for diagnostic performance of MRI, even in patients with acute or chronic renal failure. Hemodialysis reduces serum Gd concentration following exposure. A single session of hemodialysis removes 74–78 % of circulating contrast, and three consecutive sessions over 6 days eliminate up to 98.9 % [65]. However, Broome et al. described four patients who developed NSF despite receiving daily dialysis for three consecutive days starting within 24 h of contrast administration. None of these patients started dialysis immediately, with the shortest delay being 9 h [66]. The FDA advises that in patients already undergoing regular hemodialysis, there may be some benefit in scheduling a session immediately following Gd administration [60], although there is only scant evidence that this reduces the risk of NSF [67]. Initiating hemodialysis purely to eliminate Gd in renal impairment is advised against [60]. Continuous ambulatory peritoneal dialysis for 20 days clears just 69 % of the injected dose of Gd [68] and is not advised as a technique to remove Gd-based contrast agents.

Once NSF has developed, the factor most consistently associated with resolution of symptoms is improved renal function. This benefit is seen in patients with chronic renal failure who have undergone successful renal transplantation and in patients whose AKI has resolved [69]. No cases of complete remission have been described in the presence of

continued renal impairment [18]. Improvement in cutaneous changes associated with NSF in patients with improving renal function is sufficiently convincing that caution must be applied to the interpretation of results from studies reporting successful treatments for NSF in patients with concomitantly improving renal function.

Despite a myriad of other treatment options that have been proposed, the evidence is anecdotal and comes from case series and small, uncontrolled trials. No single treatment has convincingly shown consistent benefit. Physiotherapy is reported to maintain mobility in affected joints [70]. Extracorporeal photophoresis has among the largest numbers of case series but with mixed results. Studies of at least seven patients show plaque softening and improved joint mobility [71–73]. One patient with NSF for <1 year had complete regression of skin changes [71]. Mild improvement in skin tightening and range of motion was seen in only three of five patients treated in one series [73]. Other therapies with reported benefit include sodium thiosulphate [74], rapamycin [75], imatinib mesylate [76], and pentoxifylline [2]. Limited success has been seen with immune modulators, such as glucocorticoids [77], thalidomide, immunoglobulins [78], and plasmapheresis [79]. A common limitation of these studies is confounding by concomitantly improving renal function.

NSF and GFR estimation in children

Only ten children, all >6 years, have been recorded with biopsy-confirmed NSF by the Yale Registry to 2013 (personal communication, Yale NSF Registry). There is insufficient data to determine specific risk factors for NSF in children [4, 80]. Current guidelines advise against administration of high-risk Gd agents to neonates and advise caution in infants [60, 61]. This is based on the hypothesis that immature renal function in neonates and children puts them at increased risk of NSF.

Renal clearance of Gd agents occurs via passive glomerular filtration [51]. In a healthy term baby, GFR of approximately 26 ml/min/1.73 m^2 at birth increases rapidly during the first 2 weeks of life, with a slower rise until 1–2 years, at which age GFR corrected for body surface area is comparable with adult levels [81]. As nephrogenesis is incomplete until 34 weeks' gestational age, this increase is delayed for premature and very-low-birth-weight infants.

Clinical GFR estimation from serum creatinine is limited by physiologic variation between individuals in the first weeks of life, as well as inconsistent creatinine assay standardization between institutions [82]. As a result, no single method is universally employed to calculate GFR. Methods reported in a recent survey of pediatric MRI practices include application of the Schwartz formula to serum creatinine and comparison of serum creatinine with age-appropriate normal ranges [83]. Alternative markers, such as cystatin-C, may provide a more accurate estimate, but reference levels have yet to be defined for neonates [84].

No diagnoses of NSF have ever been made in neonates or infants despite thousands of Gd-enhanced MRI examinations performed. Our institution has a large pediatric renal unit, with up to 30 renal transplantations per year. Prior to 2007, Gd was used at doses of up to 0.3 mmol/kg in children with renal impairment undergoing contrast-enhanced MRA (gadopentetate dimeglumine), often as part of pretransplant workup. Between 2002 and 2007, 75 nephrology patients (neonate to 19 years of age, median 9.6 years) underwent 93 contrast-enhanced MRI scans. No cases of NSF were identified in this high-risk cohort over at least 6 months of follow-up [4]. It remains that age-appropriate GFR levels at which it is safe to administer Gd have yet to be determined (FDA Joint Advisory Committee 2008, http://www.FDA.gov).

One may speculate that NSF risk in children is not simply related to GFR. One hypothesis is that the inflammatory response to Gd is not triggered in the infant's immature immune system [18], and this raises the question of whether current guidelines are entirely justified [80]. The unwanted effect of restricting the use of contrast-enhanced MRI may be an increase in the use of computed tomography (CT) and thereby an increase in the exposure of children to ionizing radiation.

Our own experience is that it is feasible to identify children with increased likelihood of low renal function (e.g., infants, those with a history of renal disease, or children referred from certain specialties such as nephrology, urology, or oncology). This allows a simple pathway for measuring serum creatinine and estimating GFR in high-risk children, which again allows adherence to the guidelines without restricting the overall use of contrast-enhanced MRI in children. Where possible, for neonates, we suggest delaying Gd contrast administration until renal function has matured.

Alternative imaging strategies in children

Although imaging sequences in MRI are able to maximize intrinsic contrast between tissue types, Gd-based contrast agents provide further information relating to perfusion, microvascular density, and capillary permeability, information that may be invaluable. As in any aspect of medicine, the risks, benefits, and alternatives of Gd administration must be assessed. For children, options are: (1) proceed with contrast-enhanced MRI despite the risk, using lower-risk macrocyclic agents and minimizing dose, (2) perform nonenhanced MRI, adapting the imaging sequence if possible, and (3) use a different modality (ultrasound or CT) [85]. In patients with renal impairment, the risk of nephropathy caused by iodinated contrast agents used for CT should be considered before choosing CT as an alternative to MRI. The role of microbubble contrast

ultrasound in detecting microvascular and macrovascular lesions has been described in liver, carotid, and cardiac imaging. However, the potential risks of these agents are incompletely understood, and they are at present not licensed in pregnancy and children [86]. A range of nonenhanced MRI techniques are now available to depict vascular anatomy [87] and includes a technique of inverting the magnetic vector in a specific volume of tissue, then allowing time (0.5–2 s) for noninverted blood to enter this volume and finally acquire the images, which will then predominantly comprise signal from the intravascular spaces. If still using Gd-based contrast agents, good image quality is achieved with quarter-dose gadobenate-dimeglumine-enhanced abdominal MRI at 3 Tesla, although tissue contrast and objective enhancement is improved at half dose (0.05 mmol/kg) [88]. Whether this may be applied to 1.5-Tesla scanners (the most widely used field strength) and whether this further reduces the risk of NSF in renal impairment warrants further investigation. Similarly, low-dose protocols can yield good diagnostic image quality in MRA [89].

Conclusion

Although only confirmed in around 400 patients worldwide, NSF carries considerable morbidity and in rare cases may be fatal. There is a consistent body of evidence showing a significantly increased risk of NSF following Gd-based contrast-agent administration. The temporal relationship, dose–response effect, and Gd deposition in NSF plaques suggests a causal relation. Following the introduction of international guidelines limiting the prescription of Gd-based contrast agents and classifying individual agents as high, medium, or low risk, there has been reduced incidence of NSF. Ten children with NSF have been reported to date, none <6 years of age, and all developing symptoms prior to the introduction of the guidelines. Although evidence in children is scant, current guidelines extrapolate from adult data and urge extra caution in pediatric imaging. Vigilance when planning MRI, the use of nonenhanced MRI for vascular imaging, and the use of reduced-dose Gd in high-risk children are suggested as important preventative measures.

Questions (Answers provided following the reference list)

1. In relation to Gd-based contrast agents:
   a. They are used in MRI, mainly to highlight inflammation and neoplasia, and in MRA
   b. In a patient with renal impairment, Gd contrast agents are preferable to iodinated contrast media as used in CT
   c. They can be effectively removed with hemodialysis, avoiding development of nephrogenic systemic fibrosis
   d. Nonchelated Gd is highly toxic in vivo, causing encephalopathy, hemolysis, anemia, and nephrotoxicity
   e. They have a higher rate of non-NSF-related adverse events compared with iodinated contrast used in CT
2. The following statement relating to the clinical features of nephrogenic systemic fibrosis is NOT true:
   a. Features can include hyperpigmented patches, skin thickening, and joint contractures
   b. NSF may appear clinically similar to other dermatological conditions, such as scleroderma
   c. NSF typically occurs rapidly following exposure to Gd
   d. The clinical picture is variable and must be assessed in combination with histopathological features from deep-skin biopsy in order to make a confident diagnosis
   e. Clinical changes can improve following restoration of a patient's renal function
3. For patients with NSF:
   a. 15 % have a rapidly progressive course
   b. There is a 48 % mortality rate attributable to NSF
   c. Most patients become wheelchair bound due to restricted mobility
   d. There are more than 500 biopsy-confirmed cases in the literature
   e. In a patient with continuing renal impairment, no treatment has been consistently shown to improve symptoms of NSF
4. With regard to risk minimization for NSF:
   a. Dialysis following Gd contrast administration consistently prevents the development of NSF
   b. Gadodiamide (Omniscan), gadoversetamide (Optimark), and gadopentetate dimeglumine (Magnevist) are classified as high risk for NSF and are contraindicated in patients with severely impaired renal function
   c. Gd contrast agents should never be used in neonates
   d. It is safe for women to continue breast feeding following Gd administration
   e. Incidence of NSF has not dropped significantly since the implementation of guidelines limiting Gd contrast agent administration
5. Relating to NSF in children:
   a. NSF is more common in neonates and infants than in older children
   b. Creatinine blood testing is mandatory in all patients prior to Gd administration
   c. Gd use is essential to MRA
   d. Gadoversetamide (Optimark) is contraindicated in neonates
   e. Risk of NSF means that there is an absolute contraindication to the use of Gd in patients with renal impairment, and an alternative imaging modality must be used

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Answers

1. Correct answer is (a). The others are false: (b) iodinated contrast is more likely to cause transient nephropathy in patients with preexisting renal impairment; (c) hemodialysis removes Gd from the intravascular compartment, but there is scant evidence that this decreases risk of NSF; (d) these are the features of lead poisoning; (e) false

2. Correct answer is (c) Clinical features often occur after a delay, ranging from a few days to 3 years following exposure. The other statements are all true.

3. Correct answer is (e). The others are false: (a) 5 % have rapidly progressive course; (b) 48 % mortality rate over 48 months in hemodialysis patients with features of NSF compared with 20 % in patients without cutaneous disease; (c) approximately10 % are wheelchair bound; (d) just more than 400 biopsy-proven cases have been reported in the literature.

4. Correct answer is (b). The others are all false: (a) scant evidence to suggest that the risks from Gd are mitigated by dialysis; (c) EMA guidelines suggest medium- and low-risk Gd agents can be used at lowest possible dose, with a 7-day pause between scans; (d) advised to discard milk for 24 h following high-risk agents; risk–benefit analysis for lower-risk agents; (e) only five new cases (all adults) have been recorded at the Yale NSF registry since 2009 (personal communication, Yale NSF registry)

5. Correct answer is (d). The others are all false: (a) only ten biopsy-proven cases in children at the Yale Registry (all >6 years); (b) it is possible to risk profile patients to determine those that require serum creatinine measurement and/or routinely use lower risk agents; (c) noncontrast, e.g., time of flight, MRA techniques are effective; (e) always assess each case on its merits.