MRI safety; nephrogenic systemic fibrosis and other risks

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Abstract

Magnetic resonance imaging (MRI) is now a commonly used imaging modality in many neurosurgical and neurological conditions. Although generally regarded as safe, there are a number of important safety considerations. These include a recently recognised, rare condition termed nephrogenic systemic fibrosis (NSF) that occurs in patients with significant renal impairment who receive gadolinium based contrast. Currently, NSF remains poorly understood and there is no universally effective treatment beyond the avoidance of contrast in patients with significant renal impairment. Other safety considerations include MRI contraindicated devices and the role of MRI in pregnancy.

1. Introduction

Magnetic resonance imaging (MRI) is an imaging modality commonly used for neurosurgical and neurological patients for a wide variety of conditions including neoplastic, inflammatory and vascular pathologies. It is generally regarded as safe, particularly compared to CT scan, because it does not subject the patient to ionizing radiation. However, it should be noted that despite its safety, there are a number of possible risks, including that of nephrogenic systemic fibrosis (NSF), a serious side-effect associated with the administration of gadolinium-based contrast (GBC) agents in patients with significant renal impairment. Additionally, MRI utilises strong magnetic fields, and therefore some medical devices are contraindicated within the MRI unit. Table 1 summarises the main safety considerations in MRI. Table 2 demonstrates an example of an MRI safety checklist that is used to assess a patient’s safety and suitability for imaging.

2. Contrast agents

A number of contrast agents are regularly used in conjunction with MRI; with GBC agents being the most common. These contrast media are generally very safe and well tolerated. Adverse events are uncommon and a recent study suggests an adverse reaction rate of 0.46%.

2.1. Nephrogenic systemic fibrosis

A rare complication of the administration of GBC in patients with severe renal impairment was identified in 1997 and termed nephrogenic systemic fibrosis (NSF). This condition was initially known as nephrogenic fibrosing dermopathy due to its cutaneous manifestations. More recently it has been noted that this is a systemic disease and the nomenclature was modified to NSF. Despite a significant amount of research into this condition, the exact mechanism remains unclear and no single effective treatment has yet been identified. Since the first reported case, over 200 cases have been published and the characteristics of these cases are summarised in Table 3.

2.1.1. Manifestations

During the early stages of onset of NSF the patient may describe swelling, redness, pruritus and pain in the extremities. Some patients have also described muscle weakness and inflexibility of their joints. During these early stages the cutaneous findings of NSF are non-specific and commonly mistaken for cellulitis, consisting of erythema, oedema and a palpable warmth. This oedema commonly involves the lower extremities in a distal to proximal distribution resembling fluid overload. In addition to these findings asymptomatic scleral involvement has been reported in 75% of cases. These lesions in early stages appear as florid
telangiectasia and later as yellow white symmetrical scleral plaques. The non-specific nature of these findings makes early diagnosis of NSF difficult.

The later manifestations of this condition include acute plaque-like, 'woody' induration, most commonly involving the lower limbs (Fig. 1). The upper limbs and torso are less commonly affected and the face is spared (Fig. 2). The lesions are commonly pruritic or painful. In addition to the cutaneous manifestations, the condition may also affect other organs such as liver, lungs, muscles, myocardium and nerves. Death has been reported in up to 28% of patients and progression of cutaneous manifestations can result in contractures and loss of mobility.

2.1.2. Diagnosis

Diagnosis of NSF is difficult without a high index of suspicion and no laboratory tests are specific. NSF mimics other conditions, such as scleromyxoedema, and a number of investigations may be helpful in distinguishing it from these conditions. These investigations include a full blood examination, coagulation profile, blood urea nitrogen and creatinine, liver function tests, serum protein electrophoresis and biopsy of the affected areas and lesions. Histopathology in NSF demonstrates dermal fibrosis which may be histologically indistinguishable from scleromyxoedema. Early lesions of NSF consist of collagen bundles with abundant oedema separating them. With progression of the disease the collagen becomes plump and a myxoid material can be present consisting of mucin and procollagen. Immunohistochemical staining can confirm the increased number of dual-positive CD34/procollagen spindle cells. These arise from circulating fibrocytes and are usually involved in normal wound healing. It has been postulated that these cells are relocated to the dermis and other organs giving rise to NSF. Despite the non-specific findings, histopathology is still regarded as mandatory to make a diagnosis of NSF.

The diagnosis of NSF is made on the basis of these clinical findings in the setting of severe renal impairment with the administration of GBC with typical histopathological findings. The physical examination of these patients should be performed by an experienced dermatologist or rheumatologist and the

Table 2
Example of items on a MRI safety questionnaire checklist

<table>
<thead>
<tr>
<th>Category and examples</th>
<th>References</th>
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<tbody>
<tr>
<td>Ferromagnetic foreign bodies and implants</td>
<td>[7-12,15]</td>
</tr>
<tr>
<td>Aneurysm clips</td>
<td>[2,6,11]</td>
</tr>
<tr>
<td>Other</td>
<td>[2,6,11]</td>
</tr>
<tr>
<td>Implantable devices</td>
<td>[17-19]</td>
</tr>
<tr>
<td>Programmable shunts</td>
<td>[17-19]</td>
</tr>
<tr>
<td>Spinal nerve stimulators</td>
<td>[6]</td>
</tr>
<tr>
<td>Pacemakers and implantable cardiac defibrillators</td>
<td>[20-23]</td>
</tr>
<tr>
<td>Other</td>
<td>[2,6,11]</td>
</tr>
<tr>
<td>Contrast</td>
<td>[24-29]</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>[30-43,45-62]</td>
</tr>
<tr>
<td>Nephrogenic systemic fibrosis</td>
<td>[63-71]</td>
</tr>
<tr>
<td>Breastfeeding and pregnancy</td>
<td>[1,63]</td>
</tr>
<tr>
<td>Imaging in pregnancy</td>
<td>[1,63]</td>
</tr>
<tr>
<td>General risk</td>
<td>[1,63]</td>
</tr>
<tr>
<td>Anxiety</td>
<td>[1,63]</td>
</tr>
</tbody>
</table>

Fig. 1. Clinical photograph of the anterior and posterior legs of a patient with Von Hippel Lindau syndrome who developed nephrogenic systemic fibrosis after multiple contrast enhanced MRI scans of the neuraxis. Characteristic plaque-like induration is seen.
histopathology performed by a dermatopathologist. Recently, a suggested diagnostic criteria has been published based on the clinical manifestations, histopathology and the setting of advanced renal failure.16

2.1.3. Risk factors

Currently NSF has only been recorded in those patients with significant renal impairment with a glomerular filtration rate (GFR) of less than 30 mL/min/1.73 m² (Chronic Kidney Disease [CKD] stage 4 or 5) or those patients with acute renal insufficiency related to the hepatorenal syndrome or in the perioperative liver transplant period.6,17 Gadolinium has been identified in skin biopsies obtained from a number of patients with NSF which suggests a strong correlation with the development of NSF and the administration of GBC.18,19 Additionally, a particular commercial agent known as gadodiamide (Omniscan; GE Healthcare Ltd., Little Chalfont, Buckinghamshire, UK) has been noted to be associated with the vast majority of reported cases of NSF.20 Furthermore, there is the suggestion that the development of NSF is more likely with higher doses of contrast agents.20

Although an aetiological link or mechanism has yet to be described, renal dysfunction has been reported as the common predisposing factor in addition to hypercoagulability and thrombotic tendencies. All patients with a definite diagnosis of NSF either have chronic or acute kidney disease.21 The vast majority of these patients are receiving either haemodialysis, peritoneal dialysis or both. Evidence suggests that peritoneal dialysis conveys an increased risk of NSF presumably because it is less effective in removing GBC when compared to haemodialysis.22 Within the neurosurgical setting, patients at particular risk of NSF because of impaired renal function include patients with Von Hippel Lindau Syndrome, with multiple haemangioblastomas of the central nervous system requiring serial MRI and a risk of impaired renal function due to renal cysts and carcinomas (Fig. 3).

Although dose association has never been effectively examined in the literature a high dose of GBC (0.2–0.3 mmol/kg body weight) has been used in many of the patients who develop NSF23–26 and may also be a risk factor.27 It has been noted that cumulative gadodiamide exposure in dialysis patients was significantly higher among patients with NSF when compared with controls. And in addition to this both cumulative CKD stage 5 and lifetime gadodiamide exposure was significantly higher in patients with severe NSF than those patients with milder disease.28 A more recent review has identified that 90% of reported cases of NSF had received greater than the usual dose of GBC.29 This suggests that not only is an increased number of doses an independent risk factor for developing the condition, it may also increase the severity of the condition.

Additional co-factors which increase the risk of NSF have been reported and include, high doses of erythropoietin, metabolic acidosis, iron and ferritin, chronic inflammation, hypercoagulability, thrombotic events, recent vascular surgery, recent renal transplant, recent surgery, anion gap or increased phosphate, however, no universal co-factor aside from renal impairment and exposure to GBC has yet been identified.30–32 NSF appears to be equally distributed between genders.3 It has also been noted in paediatric, as well as elderly patients, although it seems to most frequently occur in the middle aged.3,5,33–35 The condition has also been identified in a wide variety of ethnicities which points against a genetic link or predisposition with this disease.3

### Table 3

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>55</td>
</tr>
<tr>
<td>Median</td>
<td>8–84</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>108 (49.1)</td>
</tr>
<tr>
<td>Female</td>
<td>112 (50.9)</td>
</tr>
<tr>
<td>Treatment of renal disease</td>
<td></td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>165 (75)</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>22 (10)</td>
</tr>
<tr>
<td>Conservative treatment</td>
<td>25 (11.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (3.6)</td>
</tr>
<tr>
<td>Cause of renal failure</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>36 (16.4)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>33 (15)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (13.2)</td>
</tr>
<tr>
<td>Adult polycystic kidney disease</td>
<td>9 (4.1)</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>8 (3.6)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>7 (3.2)</td>
</tr>
<tr>
<td>Hepato-renal syndrome</td>
<td>7 (3.2)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>91 (41.3)</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td></td>
</tr>
<tr>
<td>15 to 29 mL/min/1.73 m²</td>
<td>14 (6.4)</td>
</tr>
<tr>
<td>&lt;15 mL/min/1.73 m²</td>
<td>174 (79.1)</td>
</tr>
<tr>
<td>Not recorded/unknown</td>
<td>32 (14.5)</td>
</tr>
</tbody>
</table>

2.1.4. Prevention

Prevention of this condition is accepted to be the best strategy in combating the occurrence of NSF. This includes the use of effective measures to identify those patients at risk of NSF with impaired renal function and to avoid the administration of GBC in these patients.3 This can be prevented with care to obtain adequate investigation of renal function prior to ordering an MRI. Furthermore, patients who are at risk should have cumulative doses of contrast agents clearly documented. Through documentation and limitation of GBC administration, patients at risk have a decreased chance of developing NSF.

In those patients for whom it is unavoidable to perform contrast-enhanced imaging, contrast based CT imaging should be considered however, this poses an additional risk to the patient and may not provide sufficient detail as an imaging modality. In patients at risk of NSF, exposure to gadolinium should be limited in both duration and dose. These patients should be placed under strict observation for the onset of NSF after administration of GBC. There is no direct evidence to suggest that early-dialysis after administration of GBC reduces the risk of developing NSF, however, there is evidence to suggest that higher cumulative doses of gadolinium correlate with severe disease and thus, it would be...
Reasonable to assume that by reducing serum concentrations the patient would be less likely to develop NSF. More recent research suggests that in effectively preventing the development of NSF it is important to identify the patient's risk profile for developing NSF based on known risk factors. It is suggested that by eliminating an individual risk factor the risk of developing NSF can decrease up to 10 fold. Risk prevention strategies for NSF identified in this review were:

1) avoid high doses of GBC
2) avoid GBC in patients with acute renal failure and
3) commence dialysis early after injection of GBC
4) avoid GBC altogether where non-enhanced MRI will suffice

In addition to these measures there is evidence to suggest that some forms of gadolinium (macrocyclic forms) have a decreased risk of causing NSF and as such these compounds would be preferable for use in at-risk patients.

2.1.5. Treatment
Currently there is no universally effective treatment in patients who develop NSF. The vast majority of the literature has suggested that therapies that promote renal function may result in improvement and regression of lesions. It has been suggested that haemodialysis may assist in removal of GBC and may reduce risk of NSF, however, data are lacking to provide support for this treatment. A number of recent case reports illustrate this fact in patients who were placed on dialysis temporarily to maintain renal function. However, in many of these patients, renal function is damaged permanently and it is suggested that in these patients, transplant offers the best chance of improvement. It should be noted that even with early recognition of NSF, and improvement and maintenance of renal function, resolution may not occur. This suggests that further research is needed into treatment of NSF.

In addition to the restoration of normal kidney function, physical therapy and pain management are regarded as the mainstay of treatment of NSF. ECP is an effective treatment in the management of systemic sclerosis and NSF is regarded as an extension of this use. ECP is an immune-modulatory regimen involving treatment of leukocyte rich plasma with UV-A and a photosensitizing agent. Recently, improvement in five patients with NSF with ECP has been reported, though additional formal research is required to better assess this treatment method, its efficacy and potential side-effects.

More recent investigation has identified imatinib mesylate as effective in reducing the skin and soft tissue manifestations of NSF and this may demonstrate a further avenue for treatment. Further formal research is required to better understand the management of this condition, however due to the rarity of this condition it is acknowledged this will be difficult to achieve. Ultimately it would seem that the most effective treatment of NSF is through prevention, with the avoidance of GBC in those patients with significant renal impairment and reduced doses where MRI imaging is necessary.

2.2. Anaphylaxis
A number of case studies have reported severe anaphylactoid reactions occurring as a result of GBC administration. The incidence is very low and of the order of 0.01–0.031%. This rate is significantly less than the incidence of anaphylactic reaction that occurs with iodinated contrast which is approximately 0.031–0.157%. Recent data suggests that there may be an increased incidence of anaphylactoid reactions in those patients who have a history of allergic reactions to other contrast agents such as the iodine based contrast commonly used in CT imaging, and these reactions maybe severe and life threatening. This highlights the need for screening for past events prior to administering contrast for MRI.

3. Ferromagnetic foreign bodies and implants
MRI utilizes a strong electromagnetic field for imaging, thus, there is a risk of interference with ferromagnetic foreign bodies or implanted electro-inductive devices. This necessitates the identification of implants and devices in patients undergoing MRI and consideration of the associated risk. To deem a patient with a foreign body or implant safe to undergo MRI, the device or object...
must have undergone sufficient testing within MRI electromagnetic fields. Presently, greater than 2,300 objects have been tested for use with MRI, however, of these, only 900 items have been tested at field strengths of 3T or greater. Testing items at 3T is particularly important in the neurosurgical setting because of the increasing clinical applications of high-field-strength MRI.

3.1. Implants

A wide variety of implants are utilised in neurosurgical procedures and range from materials for cranial reconstruction to such implants as vascular clips used in the management of aneurysms and arteriovenous malformations. A large variety of materials are used to construct these implants and these materials may be ferromagnetic and thus, pose a potential safety risk or create visual artefacts during MRI. In many situations after neurosurgical intervention it may be necessary to obtain MRls, therefore it is important to determine the safety of these implants.

The use of aneurysm clips in the management of intracranial aneurysms and arteriovenous malformations is well established in neurosurgery. A number of older types of aneurysm clips are ferromagnetic and because of the risk of displacement and heating of the clip due to the electromagnetic forces, are deemed unsafe for MRI. To date only one fatality has been reported related to ferromagnetic aneurysm clips and proximity to an MRI. More recently developed aneurysm clips can be weakly ferromagnetic or non-ferromagnetic and are generally regarded as safe. However, it is essential that in each patient, the type of aneurysm clip used and its safety profile related to MRI at the correct field strength can be identified. In addition to the risk of displacement, artifacts in areas of proximity to the clips are also common and these may degrade the diagnostic accuracy of the image.

Most MRI safety tests of aneurysm clips have been conducted in 1.5 T systems. A number of aneurysm clips have also been tested at 3T. Current guidelines support imaging of most aneurysm clips at 1.5 T, providing sufficient details are obtained concerning the aneurysm clip type, manufacturer, and material and this information is correlated against current knowledge concerning aneurysm clip and MRI safety. Other implants should be identified prior to any MR procedure and current safety data reviewed to determine its safety profile. GDC coils utilised in aneurysm coiling are regarded as MR compatible.

3.2. Devices and foreign bodies

There are a wide range of devices used in neurosurgical interventions including programmable shunt valves and spinal cord stimulators. In addition to neurosurgical devices, other implantable devices such as pacemakers and implantable cardiac defibrillators must also be considered before performing MRI. Metallic foreign bodies are an additional safety consideration in MRI. Ocular foreign bodies are particularly important because of the risk of ocular damage and potential blindness. Each of these poses a safety risk through either a malfunction of the device’s mechanism or through risk of displacement due to ferromagnetic components.

Programmable shunt valves aim to optimise the opening pressure of CSF shunt systems and allow non-invasive modification of this pressure to provide individualised treatment regimens. Earlier research completed on the safety of programmable valves in MRI demonstrated no effect on valve function at 3T. More recent data, however, has demonstrated some effects due to the electromagnetic field, resulting in a “conditional” safety classification, as no permanent damage to valve function has actually been noted. A slight increase in temperature has been reported of the order of 0.4 degrees C. However, even though the shunt valve may be safe for MRI, the valve settings can change during imaging, necessitating resetting of the valve. Therefore, programmable shunt settings should be checked and adjusted after every MRI in these patients. As for other implants, significant artefacts have been reported obscuring detail of adjacent structures. Spinal cord stimulators are currently regarded as unsafe in MRI and an absolute contraindication to MRI.

Currently, MRI is contraindicated in patients with pacemaker devices or implantable cardiac defibrillators. This contraindication is due to early theoretical concerns of the effect of the magnetic field on the components of pacemaker devices and defibrillators. A number of reviews have been completed with specific data concerning the safety of these devices in MRI. More recent research has suggested that MRI can be carried out safely in special clinical circumstances in patients with more modern pacemaker devices or defibrillators.

Metallic foreign bodies also pose a safety concern because of the risk of displacement and subsequent damage of adjacent structures. Of particular note are metallic foreign bodies within the eye. On review of the literature only one reported case has described orbital injury and unilateral blindness caused by MRI in the presence of a metallic foreign body. Despite this risk, reports since this time suggest that radiographic screening for ocular foreign bodies is not necessary and clinical screening was successful in avoiding immediate, permanent, nonameliorable, or unilateral blindness.

Because of these risks, each patient should be thoroughly screened, prior to requesting MRI, for the presence of foreign bodies and devices to prevent complications, accidents and injuries. In addition, new implants and devices are constantly being developed which dictate the need for regular re-evaluation of MRI safety and testing of newly developed devices. Fortunately a number of reference texts and websites with regularly updated information about MRI compatibility of medical devices are available.

4. Pregnancy and breastfeeding

Although ultrasound is the imaging modality of choice in pregnancy, MRI is increasingly being used when a diagnosis is uncertain. MRI in pregnancy is currently regarded as safe and can be conducted during any trimester. It should be noted however, that there is very little data to support this observation and all available data is confined to 1.5 T MRI. MRI safety in pregnancy with 3T systems remains unproven. MRI during pregnancy may also give rise to the discovery of incidental abnormalities which may increase anxiety or raise ethical issues.

Generally during pregnancy non-contrast MRI is performed. GBC is not currently recommended for use during pregnancy. Research has demonstrated that GBC crosses the placental barrier and appears within the fetal bladder. From there it is excreted into the amniotic fluid and swallowed where it is potentially absorbed from the fetal gastrointestinal tract. Because of this, the fetal half-life of GBC remains unknown. Animal models have demonstrated growth retardation as a result of administration of GBC, however, no controlled human trials have confirmed this finding. As a result, GBC is regarded as a category C substance for use in pregnancy. This category includes substances for which there is evidence supporting adverse effects in the fetus from animal models, and therefore GBC should only be administered if the benefit of its use can be considered to outweigh the risk of administration.

The use of GBC during breastfeeding has also been of concern and initial guidelines suggested cessation of breastfeeding for a period of 24 to 48 hours after exposure to GBC. More recent
review of the literature suggests that only a very small proportion of the GBC is actually detectable within breast milk.82–84 Of this, only a fraction is absorbed systemically by the baby, achieving a level less than 1% of the recommended intravenous infant dose.85–87 Consequently, it is now suggested that no cessation of breastfeeding or additional precautions are required in those mothers undergoing MRI with GBC although this recommendation has not been universally accepted.81

5. Conclusion

Although MRI can generally be regarded as a safe investigation a number of important considerations have been raised concerning its safety. Particularly important is the rare but serious risk of NSF in patients with renal impairment. Care should be taken in those patients with renal impairment who require MRI with contrast and alternative imaging modalities should be used where ever possible. Patients with stage 4 or 5 CKD should avoid unnecessary administration of gadolinium and if required, the use of haemodialysis or peritoneal dialysis to maintain renal function is necessary administration of gadolinium and if required, the use of haemodialysis or peritoneal dialysis to maintain renal function is necessary.

References


85. Marti-Bonmati L, Vega T, Benito C, et al. Safety and efficacy of Omniscan (gadodiamide injection) at 0.1 mmol/kg for MRI in infants younger than 6 months of age.


