Nephrogenic Systemic Fibrosis (NSF)

An uncommon side effect of some MRI Gd-based contrast agents in patients with renal insufficiency
Introduction

Until 2006, few side-effects had been reported with gadolinium (Gd)-containing agents for MRI. These agents have been shown to be well tolerated by the vast majority of over 200 million patients exposed to gadolinium since the late 1980s: side-effects associated with Gd-chelates are usually mild to moderate in severity\(^1\). In consequence, there were considered to be among the safest agents used in humans\(^2\).

However, since a high number of articles suggest the link between some Gd-containing contrast agents and Nephrogenic Systemic Fibrosis (NSF), awareness of the potential side-effects and adverse reactions from Gd-chelates has become an important requirement for practicing radiologists and specialists because NSF, although rare, is now to be considered as a serious late adverse reaction in patients with severe to terminal renal insufficiency\(^3\).

The exact mechanism of NSF is still unknown. However, since a number of hypotheses regarding its mechanism involve their molecular structure and its consequences\(^4,5\), it is also essential to understand the chemical characteristics of Gd-chelates: the physico-chemical characteristics of MR contrast agents are regaining major interest\(^6\).
First described in the literature in 2000 as a dermatological disease and termed Nephrogenic Fibrosing Dermopathy (NFD), this disease has rapidly evolved conceptually over a short period to take into account the fact that it is a systemic disorder, and it has consequently been termed Nephrogenic Systemic Fibrosis (NSF).

It has been described only in patients with severe or end-stage renal failure. To date, there are no known cases of NSF in patients with normal renal function.

NSF is a very rare but serious disease. It involves fibrosis of the skin and connective tissues, which
can lead to contractures and joint immobility, and in some cases inability to walk (Fig. 1 and 2). NSF can occur in all age-groups and there is no predilection for a geographic region, race or gender. The vast majority of cases in the literature are adults, but NSF has also been reported in children[8].

NSF may develop over a period of days to several weeks. The skin lesions are commonly symmetrical (skin-coloured to erythematous papules that coalesce into erythematous to brawny plaques with a peau d’orange appearance. The skin becomes thickened and woody in texture[9], starting in the extremities (legs and arms), sometimes involving the trunk, but the face is always spared. Other organs may become affected later including the lungs, liver, muscles, and heart, in some cases leading to a fatal outcome.

NSF remains a challenging diagnosis and both clinical and histopathological criteria are needed to reach a specific diagnosis[10].

Since the cause and pathogenesis of NSF are still unknown, therapeutic measures with proven efficacy are lacking. Cases of improvements with extracorporeal photopheresis, plasmapheresis, ultraviolet phototherapy or intravenous immunoglobulin, etc. have been reported[11, 12]. However, the most effective treatment options available so far are related to improvement of renal function or follow renal transplant[11].
What causes Nephrogenic Systemic Fibrosis?

While a specific cause of NSF remains to be established, the pathogenesis seems to be multifactorial. Indeed, continuously emerging information contributes to improving our understanding of the pathophysiology of this new clinical entity.

With no case identified before 1997, but according to EMA (European Medicines Agency) more than 850 cases reported between 1997 and 2009, it is unclear whether NSF is a new disease or a new diagnosis. It was not until early 2006 that a possible link between prior exposure to Gd-containing contrast agents and subsequent development of NSF was made.

The mechanism by which some Gd-containing contrast agents might trigger NSF has not yet been elucidated. Several hypotheses have been proposed and discussed. The most widely accepted one is related to dechelation of less stable Gd-chelates.

Gd-chelates are mostly eliminated through the kidneys. Renal impairment will therefore delay the presence of these agents in the body. It has been speculated that it may enhance the probability of facilitating the release of the toxic free gadolinium ion (Gd³⁺) by dissociation from its chelate. Low amounts of free toxic Gd³⁺ may be progressively released in tissues and lead to the attraction of circulating fibrocytes which, subsequently, lead to a fibrosing process. A complex interplay between gadolinium and co-factors (pro-inflammatory status, vascular injury, high serum levels of calcium, phosphorus, etc.) may occur in patients with severe renal failure. In vivo dissociation of Gd³⁺ has recently been found in renally-impaired rats receiving the non-ionic linear Gd-chelate gadodiamide, but not with the ionic macrocyclic agent gadoterate. The link between dissociated Gd³⁺ and the disease remains to be demonstrated.

Two main categories of Gd-chelates are currently used: (a) “macrocyclic” chelates where Gd³⁺ is caged in the pre-organized cavity of the ligand, and (b) “open-chain” (or “linear”) chelates.

Gd-chelates differ in their thermodynamic stability constants and in their kinetic stability (e.g. half-life (T1/2) of dissociation of the complex [Gd-Ligand]). Overall, when taking into account both thermodynamic and kinetic stabilities, macrocyclic molecules are more stable than linear molecules, even more so if they are ionic.
The mechanism of NSF is still unknown. Macro cyclic molecules (such as Gd-DOTA) are considered likely to have the lowest risk of NSF. As yet, the reason for this discrepancy between macro cyclic and linear molecules remains a subject of debate.

Structure of currently marketed Gd-chelates used for MRI

<table>
<thead>
<tr>
<th>(a) Macro cyclic</th>
<th>(b) Open chain</th>
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<tbody>
<tr>
<td>Ionic</td>
<td>Ionic</td>
</tr>
<tr>
<td>Gd-DOTA, Dotarem®</td>
<td>Gd-DTPA, Magnevist®</td>
</tr>
<tr>
<td>Gd-EOB-DTPA, Primovist®</td>
<td>Gd-BOPTA, MultiHance®</td>
</tr>
<tr>
<td>Non ionic</td>
<td>Non ionic</td>
</tr>
<tr>
<td>Gd-HP-DO3A, ProHance®</td>
<td>Gd-BT-DO3A, Gadovist®</td>
</tr>
<tr>
<td>Gd-DTPA-BMA, Omniscan®</td>
<td>Gd-DTPA-BMEA, OptiMARK®</td>
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Gd-DOTA (Dotarem®), ionic cyclic gadoterate meglumine chelate, is known to form a highly stable complex, and therefore minimizes the amount of free Gd³⁺ released into the body.
Gd-based contrast agents use in patients with renal insufficiency: a cause for concern

Gd-containing agents are widely used as contrast media for MRI studies and are considered to have a good overall safety profile, when used in clinically recommended doses. They are important tools in diagnostic radiology that are particularly useful in patients with renal insufficiency.

It is important that specialists and the MR community acknowledge emerging information on NSF but at the same time consider the benefit/risk ratio prior to embarking on alternative investigations, as adults or children with chronic kidney disease require high-quality diagnostic imaging but also the safest procedure.

Consultation between radiologists and nephrologists is an important component of the management of renally-impaired patients that require imaging. It is of the utmost importance to evaluate the medical history of the patient before the administration of Gd-chelates in order to identify at-risk patients.

It is essential that radiologists and radiographers are aware of NSF. They should identify patients with severe renal impairment (ie, GFR [Glomerular Filtration Rate] or eGFR [estimated GFR] < 30 mL/min/1.73 m$^2$), and check whether the intended product is authorized in this specific population.

Physicians are advised to administer the minimal dose of contrast agent required if MR imaging with contrast is necessary, and to use the more stable agents with known lower risk.
According to the guidelines released by EMA on July 2010, the different contrast agents available on the market are at different risk of triggering NSF. Some of these contrast agents are even contra-indicated for specific population.

### High Risk contrast agents:
- Omniscan®
- Optimark®
- Magnevist®

### Medium risk contrast agents:
- Primovist®
- MultiHance®

### Low risk contrast agents:
- Dotarem®
- ProHance®
- Gadovist®

<table>
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<tr>
<th>Use during pregnancy and lactation</th>
<th>Renally impaired patients and haemodialysis</th>
<th>Liver transplant patients</th>
<th>Paediatric patients</th>
<th>Elderly patients</th>
<th>Screening for renal dysfunction</th>
</tr>
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<tr>
<td>- Use during pregnancy not recommended unless the benefit outweighs the risk</td>
<td>- Use contra-indicated in patients with severe renal impairment</td>
<td>Use contra-indicated</td>
<td>Use contra-indicated in neonates up to 4 weeks.</td>
<td>Screening of 65 years and older patients for renal dysfunction is of particular importance prior to the administration of GdCA</td>
<td>Mandatory screening for renal dysfunction by laboratory tests is required</td>
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<tr>
<td>- Discontinuation of breast feeding for at least 24 hours</td>
<td>- For patients with moderate renal impairment, use only after careful consideration of the benefit-risk ratio. If used, minimum dose should be injected and minimum of 7 days between administrations</td>
<td></td>
<td>Use in neonates should only be considered after careful consideration subject to dose and interval administration restrictions</td>
<td></td>
<td>Screening is recommended</td>
</tr>
<tr>
<td></td>
<td>- Use contra-indicated in patients with severe renal impairment</td>
<td>- Strong warnings in patients with severe renal impairment. If used, minimum dose should be injected and minimum of 7 days between administrations</td>
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<tr>
<td></td>
<td></td>
<td>- No warnings for patients with moderate renal impairment</td>
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No evidence that supports the use of haemodialysis for preventing or treating NSF in patients not already undergoing haemodialysis, but this may be useful at removing GdCA in patients already on haemodialysis.
Guerbet statement

http://www.guerbet.com/Updated_information_about_NSF.pdf

At Guerbet we contribute significantly to improving diagnosis for major disease areas (e.g. cardiovascular diseases, cancer, inflammatory and neurodegenerative diseases).

We are strongly committed to providing radiologists and cardiologists with a comprehensive range of innovative and effective contrast media to help them achieve their aim to provide optimum diagnosis for their patients.

A complete research program is in progress at Guerbet and in cooperation with recognized academic centers to better understand the mechanism of Nephrogenic Systemic Fibrosis (NSF) and thoroughly study the role of physicochemical properties of Gd-chelates in its pathogenesis. The research program includes a prospective clinical analysis of the safety of Dotarem® (commercialized under the name Magnescope® in Japan).

Fully collaborating with Health Authorities for Pharmacovigilance issues in total transparency and constantly acting in the best interests of the patients is a fundamental principle at Guerbet. This is particularly true in the case of NSF and will remain so.

Further information about NSF and Gd-based contrast agents can be found at the following websites:

European Medicines Agency (EMA): http://www.ema.europa.eu

European Society of Urogenital Radiology (ESUR): http://www.esur.org

European Society for Magnetic Resonance in Medicine and Biology (ESMRMB): http://www.esmrmb.org

International Center for Nephrogenic Fibrosing Dermopathy Research (ICNFDR), Yale University: http://www.icnfdr.org

The content of these websites corresponds to the generally held opinion of regulators, specialists or experts in the relevant field of NSF/NFD and of MR contrast agents but does not engage the responsibility of Guerbet.
References

4. 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.