

## Gadolinium and nephrogenic systemic fibrosis – What to consider for pediatric MR-imaging

Riccabona M, Dacher JN, Olsen OE, Claudon M.

Nephrogenic systemic fibrosis (NSF, or nephrogenic fibrosing dermopathy) is a recently defined disease with potentially deleterious outcome and not yet completely clarified aetiology. A common factor in many patients is an underlying kidney disease (with renal insufficiency, often on dialysis). Another commonly observed factor is gadolinium (Gd) administration, though there are patients suffering from NSF without previous known Gd exposure. Additional independent risk factors are metabolic acidosis and inflammatory and post-operative conditions.

This recently discovered and described association caused reconsideration of our use of Gd-based MR contrast material. It furthermore started a series of investigations and observations that showed other risk factors in addition to renal insufficiency [with decreasing glomerular filtration rate (GFR), and in particular with GFR less than 30 units (ml/min/1.73m<sup>2</sup>): repeated or/and high Gd dose particularly using the less stable linear Gd compounds such as Omniscan® and Magnevist®. However, there are a few reports of patients developing NSF even after exposure to cyclic Gd derivatives. Though most patients are adults, there are a few cases published describing children with NSF - at present only partly linked with Gd exposure. Nevertheless, this new insight urges the paediatric radiology community to consider this aspect when performing MRI, and recommendations on how to proceed with this issue are frequently discussed.

The FDA, pharmaceutical groups and companies as well as a number of major hospitals have issued statements that suggest a careful use of Gd-based contrast agents, particularly in infants (due to the physiological immature kidney in the first weeks of life); some drugs (i.e. Magnevist® and Omniscan®, both linear Gd compounds) have had their approval for use in the first year of life withdrawn. In order to properly address the potential risk of Gd administration, some precautions have to be taken.

With current knowledge, and considering the current discourse, we suggest these main points of action:

1. Reconsider the need of MR. More sophisticated and dedicated ultrasound investigations can probably solve a number of problems answering the therapeutically relevant questions thus making MR unnecessary.
2. There are situations where the use of contrast-enhanced MR should be reconsidered; sometimes unenhanced MR-scans using new techniques can solve the problem. Performing CT is associated with radiation burden and contrast induced nephropathy (CIN) and thus needs to be considered very carefully when used as alternative imaging.
3. Precautions have to be taken to identify patients at increased risk for NSF, i.e., patients with renal disease or with liver transplantation. Some centres primarily rely on history and clinical data, other centres ask for a recent blood sample to prove normal creatinine (as often also done for contrast enhanced CT). Estimated GFR in children may be calculated as (the height of the child [cm] x 33 / serum-creatinine [ $\mu\text{g/l}$ ]).
4. In all patients with a potential renal disease or impaired renal function as well as in patients with inflammatory conditions and acidosis, GFR measurements or estimates should be performed and – if below 30 – the indication for contrast-enhanced MR should be reconsidered and discussed on an individual base in tight collaboration with the attending nephrologist. If (estimated) GFR is between 30 and 60, Gd should be administered with caution. Patients and their parents have to be informed about the potential risk and an informed consent should be obtained prior to the investigation.

5. Particularly in patients with an increased risk for NSF, also including infants, only macro-cyclic Gd compounds should be used, as they are more stable and presently are considered to bear a lower risk of inducing NSF.
6. As repetitive applications potentially leading to a high cumulative systemic Gd dose appear to be a risk factor, reduction of repeated investigations and basically single dose techniques should be promoted. The cumulative Gd dose of a patient should be recorded and noted, e.g. in patient's file, and a thorough follow-up - particularly in risk patients - over a longer period of time should be established.
7. Supportive measures for preventing NSF are balancing acidosis, hydration and improvement of renal function prior to administration. However, all these measures – particularly dialysis - do not guarantee full protection.
8. However, all this should not be exaggerated, and thus we should not deny any child a well indicated MR study that offers therapeutically or prognostically essential information.