Nephrogenic systemic fibrosis: new guidelines

Fibrose nefrogênica sistêmica: novas diretrizes

*Claudia da Costa Leite**

In a previous editorial[1] I had already approached nephrogenic systemic fibrosis (NSF). At that time, there was considerable panic in relation to this new disease mainly because at that time current paradigm on the total safety of gadolinium as a contrast medium had been broken.

NFS is still an extremely severe and often fatal disease, still without an effective treatment. However, the risk group likely to develop such condition is more restricted than initially thought. This is a promising fact, as many diseases diagnosis are highly dependent upon magnetic resonance imaging (MRI) with the use of gadolinium as their most effective diagnostic tool, and not using such contrast medium many times would compromise the diagnostic capabilities of the method[2,3].

With the notification and observation of NSF cases over the past few years, new guidelines for the use of gadolinium in patients with renal failure (RF)[2] have been established. Nowadays, in the usage directions of gadolinium-based paramagnetic contrast agents, there are restrictions for use in patients with severe acute or chronic RF (estimated creatinine clearance < 30 mL/min/1.73 m^2) and in patients with acute RF (ARF) at any severity level, as well as in patients with ARF related to hepatorenal syndrome or postoperatively to liver transplant. It is important to remind that the gadolinium effect is not related to a single administration of such agent, but to the cumulative dose administered to the patient.

The new guidelines for the use of gadolinium vary according the origin of the group responsible for such guidelines. There are basically two groups: the North American and the European ones. While the North American group does not take into consideration the type of gadolinium being used, establishing generic procedures for the use of such contrast agent, the European group establishes different standards according with the type of gadolinium intended for use[2].

North American guidelines[2]

It is primarily suggested that during the interview prior to the MRI examination, a question on the presence of renal disease should be included. In positive cases, it is necessary to ask whether or not the patient is being submitted to dialysis. In the case of chronic RF (CRF), the patient should be warned on the risks associated with intravenous injection of gadolinium, following a careful evaluation of the risk/benefit ratio of such procedure.

For patients with grades 1 and 2 RF (estimated creatinine clearance between 60 and 90 mL/min/1.73 m^2), it is suggested that gadodiamide (Omniscan®) **should be avoided.**

When the risk/benefit ratio favors the performance of MRI in patients with grade 3 RF (estimated creatinine clearance between 30 and 59 mL/min/1.73 m^2), the use of the lowest possible dose shall be considered, while assuring the diagnostic value of the images (if possible, half the dose, especially when a 3 tesla MRI apparatus is available).

In hemodialyzed patients, the possibility of performing a hemodialysis session right after the gadolinium injection should be considered, followed by another session after 24 hours, whenever possible. Peritoneal hemodialysis patients require even greater care, and the need to administer gadolinium to such patients shall only be considered after extensive and thorough ponderation.

In cases of patients with grades 4 and 5 RF (estimated creatinine clearance < 30 mL/min/1.73 m^2), the administration of gadolinium is more problematic, and it should be further considered that the administration of iodinated contrast agents for such patients may compromise the renal function even further, which makes the diagnostic procedure for such patients even more difficult.

Progressively, in the comparison between grade 3 RF patients and those with grades 4 and 5 RF, the discussion of risk *versus* benefits leans in favor of the risks, which are greater in this later subgroup. With dialytic patients, when the decision that the benefits are greater than the risks is made, a dialysis schedule similar to that for patients with grade 3 CRF is suggested.

As a general rule, in the case of patients with estimated creatinine clearance < 15 mL/min/1.73 m^2, gadolinium injection should be avoided.

In cases of ARF, the possibility of waiting for an improvement of the renal function should be considered before those patients are submitted to contrast-enhanced MRI. Particular care is to be taken with patients with hepatic in-

* Associate Professor, Department of Radiology at Faculdade de Medicina da Universidade de São Paulo (FMUSP), Head of the Neuroradiology and Magnetic Resonance Imaging Section, Instituto de Radiologia do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (InRad/HC-FMUSP), São Paulo, SP, Brazil. E-mail: claudia.leite@hcnet.usp.br

sufficiency (hepatorenal syndrome) and postoperatively with liver transplant patients.

In summary, grade 3 patients (estimated creatinine clearance between 30 and 59 mL/min/1.73 m^2) were considered as presenting low risk for developing of NSF at a dose of 0.1 mmol/kg (habitual) or less. There is no evidence of risk for developing NSF in patients with estimated creatinine clearance > 60 mL/min/1.73 m^2, and in such cases the use of gadolinium at the habitual dose of 0.1 mmol/kg, or lower, is safe.

European guidelines[2]

The European Society of Urogenital Radiology (ESUR) Contrast Media Safety Committee has defined the indications for the use of gadolinium at MRI, which were later adopted by the European Society of Magnetic Resonance in Medicine and Biology (ESMRMB).

Both entities have considered the use of gadolinium as a high-risk procedure for patients with grades 4 and 5 CRF (estimated creatinine clearance < 30 mL/min/1.73 m^2), including those requiring dialysis, and those with a reduction of the renal function that were or will be submitted to liver transplant. Lower risk patients would be those with grade 3 CRF (estimated creatinine clearance between 30 and 59 mL/min/1.73 m^2) and infants with less than one year of age.

The European guidelines have also established the procedures according with the type of gadolinium that is intended to be used, and therefore, for each different type, a particular instruction is to be followed.

The following types of gadolinium-based contrast agents – gadodiamide (Omniscan®), gadopentetate dimeglumine (Magnevist®) and gadoversetamide (Optimark®) – **are contraindicated** for patients with grades 4 and 5 CRF, even for those undergoing dialysis, and those with reduction of renal function that were or will be submitted to liver transplant. These contrast agents are to be used with caution in patients with grade 3 CRF and in infants with less than one year of age. The ESUR suggests that the creatinine levels be measured in all patients prior to the administration of any of these three types of gadolinium.

The contrast agents presenting intermediate risk associated with NSF are: gadobenate dimeglumine (Gd-Bopta®), gadofosveset trisodium (Vasovist®) and gadoxetate disodium (Primovist®). These agents can be utilized in lower doses with similar effectiveness, and except for patients with grades 4 and 5 RF, it is not necessary to measure creatinine levels for the use of such agents.

The contrast agents containing gadolinium with low risk NSF development are gadobutrol (Gadovist®), gadoterate meglumine (Dotarem®) and gadoteridol (Prohance®). Regardless of the renal function, the entity suggests that the lowest possible diagnostic dose be utilized, and that, under appropriate clinical indications, gadolinium can and should be utilized as a robust diagnostic tool.

Final remarks

Recent studies have demonstrated that there is a reduction of the risk for developing NSF with a parsimonious utilization of paramagnetic contrast agents, including the correct dosage – the lowest possible while assuring the acquisition of images with appropriate diagnostic value[4,5].

As seen above, there are procedure variations, but according to both the European and North American guidelines, patients with estimated creatinine clearance > 30 mL/min/1.73 m^2 may receive gadolinium although with appropriate caution regarding the administered dose. Caution is also suggested for the use in infants with less than one year of age.

In the cases of grades 4 and 5 CRF, in spite of the fact that in both guidelines such cases are considered **risk groups for the development of NSF,** the guidelines vary, but one can notice that common sense is of paramount importance when evaluating risks *versus* benefits. These orientations are also applicable to ARF, with particular caution in cases of hepatorenal syndrome.

This is a discussion of utmost importance, considering that in patients with severe RF that cannot be submitted to contrast-enhanced MRI, the other diagnostic imaging method applicable is contrast-enhanced computed tomography that, besides radiation exposure and risks associated with iodinated contrast agents, also poses the risk of iodinated contrast-induced nephropathy[6].

REFERENCES

1. Leite CC. Gadolínio e fibrose nefrogênica sistêmica: o que todo médico deve saber. Radiol Bras. 2007;40(4):iv–v.
2. Thomsen HS. How to avoid nephrogenic systemic fibrosis: current guidelines in Europe and the United States. Radiol Clin North Am. 2009;47:871–5.
3. Marckmann P, Skov L. Nephrogenic systemic fibrosis: clinical picture and treatment. Radiol Clin North Am. 2009;47:833–40.
4. Martin DR, Krishnamoorthy SK, Kalb B, et al. Decreased incidence of NSF in patients on dialysis after changing gadolinium contrast-enhanced MRI protocols. J Magn Reson Imaging. 2010;31:440–6.
5. Altun E, Martin DR, Wertman R, et al. Nephrogenic systemic fibrosis: change in incidence following a switch in gadolinium agents and adoption of a gadolinium policy – report from two U.S. universities. Radiology. 2009;253:689–96.
6. Martin DR. Nephrogenic systemic fibrosis: a radiologist's practical perspective. Eur J Radiol. 2008;66:220–4.