

Gadolinium accumulation after contrast-enhanced magnetic resonance imaging: what rheumatologists should know

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Magnetic resonance imaging (MRI) is an imaging modality capable to explore all anatomic areas of the human body, with the great advantage of avoiding ionizing radiation exposure. In the joints, MRI is the modality of choice in the evaluation of cartilage, joint space, and synovium and is excellent in evaluating all periarticular structures. MRI has gained an increased importance in rheumatology, mainly for the possibility of early diagnosis and evaluation of disease activity in patients with seronegative spondyloarthropathies involving the spine [1]. In addition, a baseline evaluation of the hand and wrist in patients with rheumatoid arthritis (RA) is considered useful by many rheumatologists because it can evaluate synovitis, ero-

sions, and bone marrow edema (BME) with a single examination [2]. The European League against Rheumatism (EULAR) recommendations on imaging in RA suggest that MRI can be useful to: confirm the diagnosis of RA by showing synovitis in clinically unaffected joints; predict the severity and progression of RA; and assess residual synovitis in RA patients in clinical remission [3]. The sensitivity in detecting erosions of the RA wrist is higher for MRI than for radiography. As a result, MRI has been accepted by both the Outcome Measures in Rheumatology (OMERACT) [4] and the American College of Rheumatology [5] for the evaluation of structural damage in clinical trials studying novel therapeutic agents in RA and in psoriatic arthritis. BME is a significant predictor of negative prognosis in patients with early, undifferentiated arthritis and in those with established RA [6]. Finally, synovitis can be visualized comparing unenhanced and contrast-enhanced static images but also by dynamic MRI, i.e., following the course of contrast enhancement during the time after injection [7]. All the previous aspects are summarized in a composite score, the rheumatoid arthritis MRI scoring system (RAMRIS), which is used during MRI follow-up of RA patients [8]. In the real world, few patients outside industry-sponsored clinical trials to test the efficacy of new drugs perform a regular follow-up by contrast-enhanced MRI. However, since very often the standards employed in controlled clinical trials are subsequently transferred to everyday clinical practice [9], it is possible that MRI will be more frequently used in RA in the next future.

Using static and variable magnetic fields and non-ionizing radiofrequency radiations, MRI has been traditionally regarded as a safe imaging modality in rheumatology, only limited by the presence of absolute contraindications such as the presence of MR-unsafe devices in patient's body. Contrast agents used in MRI are mainly based on paramagnetic substances, capable to locally change the relaxation times of

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tissues where they are concentrated after intravenous injection. The most used contrast agents are metal ion-ligand complexes, composed of a gadolinium ion (Gd^{3+}) bond with a chelating agent; Gd^{3+} shortens the longitudinal relaxation time of water protons [10]. The chelating ligand overcomes the direct toxicity by free Gd^{3+} maintaining its contrast properties and influences the biodistribution of the drug. Gadolinium-based contrast agents (GBCAs) may have different chemical structures with different degrees of stability of the Gd-chelating agent complex [11]. Initially, GBCAs were introduced in clinical practice to improve the detection and diagnosis of central nervous system diseases; only later, their utility has been recognized and approved in other fields, including not only oncologic imaging all over the body but also the evaluation of chronic and acute inflammatory conditions [12].

Since their introduction in the 1980s, GBCAs were administered with few restrictions and with the awareness of minimal patients' risk [13]. Nevertheless, 10 years ago, the identification of nephrogenic systemic fibrosis (NSF) as a possible non-allergic adverse effect of GBCAs administration to patients with renal impairment changed the clinical practice [14]. NSF is a rare disease characterized by skin thickening and fibrotic changes in various organs, ranging from mild clinical features to fatal conditions [14, 15]. The GBCAs with greatest risk of NSF have been reported to be gadopentetate, gadodiamide, and gadoversetamide. To date, all these GBCAs are contraindicated in patients with estimated glomerular filtration rate (eGFR) <30 mL/min/ 1.73 -m², while the other GBCAs should be administered with caution [16]. These recommendations have substantially reduced to zero the new cases of NSF over the past few years.

Although the presence of renal impairment is a necessary requirement for the occurrence of NSF, Gd^{3+} accumulation in human tissues has been well demonstrated in patients with normal renal function. Evidences about Gd^{3+} accumulation after multiple injections of GBCAs has been known for 10 years, being described first in the bone using mass spectroscopy on hip specimens taken during hip replacement surgery [17]. However, Gd^{3+} accumulation in the bone has not been reported in vivo so far. Only in the last 3 years, Gd^{3+} deposition became a hot topic, when Gd^{3+} accumulation has been described in intracranial structures. First evidences of Gd^{3+} deposition in brain were reported in studies on MRI by Kanda et al. [18] and Errante et al. [19], and later confirmed by different groups [20]. Gadopentetate dimeglumine and gadodiamide were the molecules most frequently associated with signal increase in brain nuclei. Studies reported that this effect can be appreciated after about five injections of the recommended dose of 0.1 mmol/kg.

Beginning from the qualitative clue of a signal intensity increase in cerebellar dentate nucleus, these authors discovered a statistically significant quantitative change on T1-weighted images after multiple GBCAs administrations, not

only in dentate nucleus but also in globus pallidus and other brain structures. So far, it is not clear in which chemical form Gd is accumulated.

Several factors may influence Gd^{3+} release, occurring most likely through a process of “transmetallation” induced by the presence of metals with high affinity for Gd^{3+} such as Fe^{3+} , Ca^{2+} , Zn^{2+} , or ligands such as phosphate [21]. Despite attempts to find a common mechanism of deposition have failed, mass-spectroscopy analysis on autoptic specimens of patients who underwent multiple GBCA injection demonstrated the presence of variable Gd^{3+} levels in various human tissues, especially the bones, kidneys, skin, and brain [20, 22]. So far, Gd^{3+} accumulation in the brain has been mainly demonstrated only in the brain of patients undergoing MRI scans for the diagnosis of neurological diseases. Research is needed for evaluating Gd^{3+} accumulation in the brain of patients undergoing multiple contrast-enhanced MRIs for non-neurological purposes, such as rheumatologic patients. In fact, while Gd^{3+} brain accumulation in patients with neurological diseases may be related to a blood-brain barrier damage (frequent in diseases such as multiple sclerosis), studies showed GBCA effect related to Gd^{3+} accumulation also after excluding patients with potential blood-brain barrier damage [23]. Thus, it can be argued that all patients undergoing multiple administrations of GBCAs are at risk of Gd^{3+} accumulation in the brain, regardless of the underlying pathology or anatomical district being investigated using MRI.

Studies in the last year tried to differentiate gadolinium deposition on the basis of the grade of dissociation from the ligand. Macrocyclic GBCAs have been shown both in vitro [24] and in vivo [25] to have lower releasing rate compared with linear ones, and could produce less deposition in human tissues.

On the other hand, the clinical significance of Gd^{3+} accumulation is still unclear. Various potential mechanisms of Gd^{3+} accumulation toxicity have been postulated, including the induction of release of profibrotic and proinflammatory chemokines and cytokines, oxidative stress, transmetallation, and competition of Gd^{3+} with Ca^{2+} [26]. To date, few clinical effects have been demonstrated, especially nephro-, hemato- and neuro-toxicity on animal studies, frequently using very high doses, but only few case reports of neuro- and nephrotoxicity on humans have been published [26]. Recently, Semelka et al. evaluated the clinical aspects of Gd^{3+} accumulation in patients with normal renal function and termed this occurrence as “gadolinium storage condition”. They reported that patients might experience skin thickening and bone/chest pain after administration of GBCAs [27]. They thus identify a new pathologic entity defined as “gadolinium deposition disease”, which may share clinical features with NSF but also present with other, non-typical symptoms [28]. It is interesting to note that awareness of patients on the topic is increasing over time, as several patient advocacy groups on “gadolinium toxicity” have been recently established in the USA [29].

Future studies should be focused on possible clinical consequences of multiple GBCAs administrations and options to reduce Gd^{3+} accumulation. N-acetyl-cysteine or iron chelation pre-treatments have been proposed for reducing Gd^{3+} toxicity [26]. Furthermore, alternative options for the quantitative and objective assessment of joint inflammation with MRI avoiding GBCA injection such as diffusion-weighted imaging, T1 and T2 mapping, and MRI-ultrasound-Doppler fusion images may be considered [30].

In conclusion, MRI with the intravenous administration of GBCAs is useful in the assessment of rheumatologic conditions. So far, Gd^{3+} accumulation in the brain has not been associated with any clinical consequences. However, the rheumatologic community should be aware of the potential risks of repeated administrations of GBCAs.

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