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CONTRAST MEDIA

Gadolinium retention in the body: what we know and what we can do

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Abstract Gadolinium-based contrast agents (GBCA), widely used in Magnetic Resonance Imaging (MRI) for almost 30 years, were recently shown to be deposited in the brain and to induce persistent T1 shortening in deep gray matter structures in subjects with normal renal function. The aim of the present study is to summarize the evidence derived from the rapidly growing scientific literature on Gadolinium retention in the brain and in the rest of the body. To this end, the original articles that described imaging and pathology findings in humans and animals exposed to GBCA were reviewed. The main aspects that emerged were the different effects of linear and macrocyclic GBCA on brain MRI appearance, the evidence of Gadolinium tissue retention in multiple organs, and the debated issue of the possible clinical consequences. Although no adverse health effects have been documented so far, updated information about GBCA build-up in the body is necessary for health professionals, also in view of the increasing concern in the general population. To date, our knowledge about the mechanisms of Gadolinium tissue deposition and, above all, its long-term consequences is still largely incomplete. However, while official guidelines are eagerly awaited, some advices may already be given, to help our radiological daily practice.

Keywords Gadolinium-based contrast media · MRI · Dentate nucleus · Gadolinium retention · Toxicity

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Introduction

Gadolinium-based contrast agents (GBCA) are chemical compounds used in magnetic resonance imaging (MRI) to exploit their paramagnetic properties, i.e., their capability to regionally alter the MRI signal of the biological compartment in which they accumulate.

Gadolinium (Gd) is a paramagnetic lanthanide heavy metal, that, in its free ionic form (Gd^{3+}), can compete with Ca^{2+} and become toxic in biological systems [1]; therefore, it must be chelated to an organic ligand. Commercially available GBCA contain Gd chelated in different forms, are usually administered intravenously, and have been used in over 100 million patients in the last 29 years [2] and in roughly 30–45% of all clinical MR studies today [3]. GBCA are credited with an excellent safety profile, as very few, and mostly mild, acute adverse reactions have been reported, despite the large and prolonged use (0.08–0.12%) [4, 5].

Once administered, GBCA are eliminated from the body through the urinary, and, to a lesser extent, biliary system. In subjects with normal renal function, they are usually cleared from the blood in about 1.5 h, and completely recovered from the urine in 7 days (>90% in the first 12 h) [6].

GBCA can be divided into linear and macrocyclic types, the latter being considered more stable. Indeed, macrocyclic GBCA form cage-like structures with Gd^{3+} enclosed in the cavity of the complex and tend to have lower dissociation constants [7]. The higher the dissociation constant, the more likely free Gd can be released into the circulation and tissues [8].

Between 2006 and 2009 a safety issue emerged for GBCA, as Nephrogenic Systemic Fibrosis (NSF), a

subacute/chronic disease associated with significant morbidity, was described and put in relation to previous administration of some linear GBCA in patients with renal dysfunction [3]. However, once a careful evaluation of the renal glomerular filtration rate (GFR) has been imposed as a pre-requisite to perform a contrast-enhanced (CE) MRI scan, the incidence of new NSF cases has almost disappeared [9].

Since 2014, a new safety concern regarding the use of GBCA has spread over the scientific community: the evidence, and the possible consequences, of long-term retention of GBCA in the brain after multiple CE-MRI in subjects with normal renal function. In fact, there are consistent and ever-growing imaging and histopathologic findings of Gd accumulation in individuals with normal GFR who had received, even years earlier, multiple GBCA administrations.

In this review, we focused on original articles published in peer-reviewed journals in the last 3 years, aiming to: (I) summarize the latest evidence deriving from human and animal studies on Gd retention in the body, (II) evaluate the methodological aspects of the imaging findings reported so far and (III) critically address the issue of the possible clinical consequences of the existing data. Finally, some suggestions on the effects of this increased knowledge on our radiological daily practice are presented.

Gadolinium retention in the brain: imaging findings

Most CE-MRI brain acquisitions exploit the property of GBCA to shorten the T1 relaxation time of living tissues after extravasation in the interstitial space. In the central nervous system (CNS), this was initially believed to happen almost exclusively in areas with altered blood–brain barrier (BBB). However, it is now clear that intravenously injected Gd can slowly pass an intact BBB, with mechanisms possibly involving transmetallation, specific metal transporters, or even a pathway through the CSF, perivascular spaces and the glymphatic system [3, 10]. In T1-weighted (T1w) images, contrast-enhancing lesions appear hyperintense respect to the surrounding, unenhanced brain. This signal change usually persists up to 30 min, although sporadic extended persistence has been reported [11].

In the past 3 years, several papers reported the presence of spontaneous high signal intensity (SI) in unhenanced T1w images of the brain, mainly localized in deep gray matter structures such as dentate nuclei (DN) and globus pallidus (GP), in patients with normal renal function, all with a history of prior exposure to multiple GBCA administrations (Fig. 1).

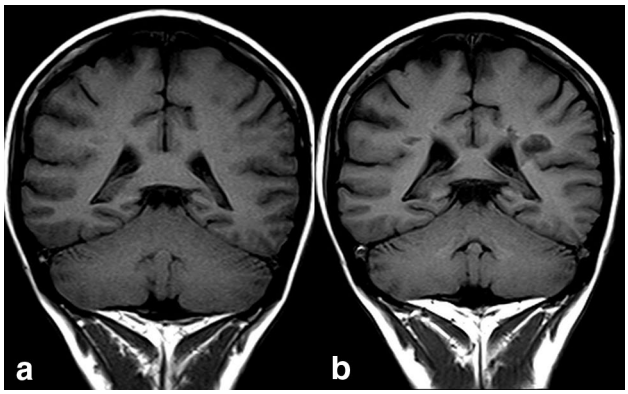

Fig. 1 Change in dentate nuclei signal intensity after multiple CE-MRI with linear Gadolinium-based contrast agents. Unenhanced coronal SE T1-weighted images in a patient with relapsing–remitting multiple sclerosis at diagnosis (**a**) and in a follow-up study 6 years later (**b**), after 6 injections of Magnevist®. The cerebellar dentate nuclei, initially isointense to the surrounding brain, show homogeneous bilateral and symmetrical T1w-hyperintensity at the follow-up scan. Also note worsening of the supratentorial demyelinating lesions, leading to increased axonal loss

The pioneering publication was a retrospective study in 19 brain tumor patients, who underwent at least 6 examinations with linear GBCA (gadopentate dimeglumine, Magnevist® and/or gadodiamide, Omniscan®), compared with 16 patients who received at least 6 unenhanced MRI [12]. In that study, only patients exposed to GBCA showed T1 shortening of deep gray matter nuclei, with an increase in the DN-to-pons (DNP) and GP-to-thalamus (GPT) SI ratios significantly correlated with the administered dose.

Afterwards, higher DNP SI after repeated administrations of Omniscan® has been described in relapsing–remitting multiple sclerosis (RR-MS) and meningioma patients, even after <6 GBCA administrations, with a dose–response relationship [13, 14].

Later, DN T1 shortening was associated with prior repeated exposure to Magnevist®, but not to the nonionic macrocyclic Gadoteridol (ProHance®) [15]. This important difference between linear and macrocyclic GBCAs was confirmed by other studies that assessed DN and GP SI in patients undergoing multiple MRI scans with Magnevist® or Gadobenate Meglumine (MultiHance®) vs those receiving Gadoterate Dimeglumine (Dotarem®) or Gadobutrol (Gadovist®); again, a dose-dependent T1 shortening effect was observed only for linear GBCAs [16–20]. This different behavior of the two GBCA classes supports the hypothesis that the observed T1 shortening is related to dissociation of the Gd ion from its chelating ligand molecule [21]. Table 1 lists the main features of the GBCA approved for CNS imaging along with the corresponding findings reported in imaging and pathology studies in humans and animals with a normal renal function.

Table 1 Summary of product characteristics of the Gadolinium-based contrast agents used for central nervous system imaging and of the articles reporting MRI and histopathologic findings in humans and animals without nephrogenic systemic fibrosis

Trade name	Omniscan®	Magnevist®	MultiHance®	Optimark®	Dotarem®	ProHance®	Gadovist®
Generic name	Gadodiamide	Gadopentetate dimeglumine	Gadobenate dimeglumine	Gadoversetamide	Gadoterate meglumine	Gadoteridol	Gadobutrol
Company	GE- Healthcare	Bayer	Bracco	Mallinckrodt	Guerbet	Bracco	Bayer
Structure	Linear	Linear	Linear	Linear	Macrocyclic	Macrocyclic	Macrocyclic
Ionicity	Nonionic	Ionic	Ionic	Nonionic	Ionic	Nonionic	Nonionic
Stability	Low	Intermediate	Intermediate	Low	High	High	High (kinetic), Low (thermodynamic)
NSF risk*	High (75% of reported cases)	High (23% of reported cases)	Intermediate	High	Low	Low	Low
Clearance	Renal	Renal	96% renal, 4% hepatic	Renal	Renal	Renal	Renal
R1 Relaxivity, 1.5T[a]	4.3	3.9–4.1	6.3–7.9	4.7	3.6	4.1	4.7–5.2
R1 Relaxivity, 3T[a]	4.0	3.7–3.9	5.5–5.9	4.5	3.5	3.7	4.5–5.0
MRI findings							
DN T1 shortening (humans)	Yes: 12–14, 22, 23, 31, 36, 45	Yes: 12, 15, 17, 19, 26, 28, 30-34, 36, 48, 50 (R1), 54 (R1)	Yes: 18, 20, 36, 61; No: 22		No: 16, 17, 19, 31, 43	No: 15	No: 16, 18, 19, 26-28, 31, 44 (R1); Yes: 25
GP T1 shortening (humans)	Yes: 12, 22, 36, 45; No: 31	Yes: 12, 17, 33, 36, 54 (R1); No: 31, 32	Yes: 36; No: 22		No: 17, 31		No: 18, 27, 31; Yes: 25
DCN T1 shortening (animals)	Yes: 29 (3–24 days pi), 40 (72 h pi, R1), 62 (5 weeks pi), 63 (10 weeks pi, R1)	Yes: 63 (10 weeks pi); No: 29 (3–24 days pi)	Yes: 29 (3–24 days pi), 63 (10 weeks pi)		No: 29 (3–24 days pi), 62 (5 weeks pi), 63 (10 weeks pi)		No: 29 (3–24 days pi)
GP T1 shortening (animals)	No: 29 (3–24 days pi)	No: 29 (3–24 days pi)	No: 29 (3-24 days pi)		No: 29 (3–24 days pi)		No: 29 (3–24 days pi)
Tissue deposition							
Brain (humans)	Yes: 45, 59, 60	Yes: 60	Yes: 60, 61			Yes: 61	Yes: 61
Bone (humans)	Yes: 68–70		Yes: 61			Yes: 61, 68-70	Yes: 61
Skin (humans)	Yes: 77; No: 78	Yes: 77; No:78	Yes: 61, 77			Yes: 61, 77	
Brain (animals)	Yes: 40 (7 days pi), 46 (24 h pi), 62 (5 weeks pi), 64 (3–45 days pi), 65 (7 days–20 weeks pi)	Yes: 46 (24 h pi), 66 (7 days–20 weeks pi)	Yes: 46 (24 h pi)		Yes: 46 (24 h pi), 62 (5 weeks pi)	Yes: 46 (24 h pi)	Yes: 46 (24 h pi)
Bone (animals)	Yes: 40 (7 days pi), 80 (5 days pi), 81 (10 weeks pi)						
Skin (animals)	Yes: 80 (5 days pi), 81 (10 weeks pi)						

DN Dentate Nuclei, *GP* Globus Pallidus, *DCN* deep cerebellar nuclei, *pi* post last GBCA injection, *R1* measurement of T1 relaxation rate. Figures in the lower part of the Table are the references numbered according to their appearance in the text. Modified from [41]

* Nephrogenic Systemic Fibrosis risk according to the European Medicines Agency (Assessment report for gadolinium containing contrast agents, http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_31/WC500099538.pdf. Published 1 July 2010)

[a] Values in l $mmol^{-1}$ s^{-1} (plasma, 37 °C)

Since 2014, some conflicting findings have also been reported. For example, multiple injections of MultiHance® were associated with significantly lower DN/middle cerebellar peduncle and GPT T1w-SI ratios compared to patients who received (also) Omniscan® [22, 23]. Conversely, in another study, MultiHance® induced increased DNP T1w-SI ratio [20]. Possible explanations for this discrepancy may include differences in the amount of Gd given or in the image analysis. As for Gadovist®, which has high kinetic stability coupled to a relatively low thermodynamic stability [8, 24], one report claiming that increased DNP and GPT SI ratios were present in MS patients who received >4 injections [25] has been heavily criticized, and its findings were not replicated in other subsequent studies that analyzed SI changes after administration of this GBCA in humans [18, 19, 26–28] and animals [29].

The DN consistently represented the major site of increased SI in the brain after multiple linear GBCA administrations in several studies [12, 15, 19, 26, 28, 30–36]. The reason for such susceptibility may be related to the fact that DN are preferential sites of accumulation of metallic ions and calcium [37, 38], as well as to their proximity to the choroid plexus of the fourth ventricle, which is known to sequester toxic heavy metals and metalloid ions [39]. One may thus speculate that a transport mechanism mediates the preferential accumulation of Gd in some brain regions, using the blood/CSF barrier as a passageway toward the interstitium [40].

The intriguing observation that, by increasing the administered GBCA volume, Gd accumulation becomes evident in other brain sites involved in the deposition of minerals and metallic ions also supports this hypothesis [41]. In fact, in 13 patients who received at least 35 doses of linear GBCA, a significant T1w hyperintensity was evident not only in DN and GP, but also in the substantia nigra, posterior thalamus, red nucleus, colliculi, superior cerebellar peduncle and caudate nucleus [36]. Probably, higher doses can saturate the most common sites of deposits, resulting in a more complex Gd distribution [10]. In a patient who had undergone >80 CE-MRI with mixed (linear and macrocyclic) GBCA, T1w hyperintensity was observed not only in DN and basal ganglia, but also in the cortex around the central and calcarine fissures [42]. Conversely, no evidence of significant T1 shortening was observed, both using "conventional" SI [16, 43] and relaxometry [44] methods, even after massive cumulative doses of macrocyclic GBCA. However, it should be remembered that the T1 shortening detectable by MRI does not by any means linearly reflect the actual amount of Gd deposited in the brain, as, on one hand, some Gd may be present in a "magnetically inert" (i.e., insoluble) form, and, on the other hand, tiny amounts of Gd, likely without biologic effect, may induce striking MRI evidence.

Imaging of gadolinium retention in the brain: methodological considerations

A better understanding of the Gd-related MRI changes in the brain requires the analysis of the imaging techniques used.

Most studies on SI changes evaluated T1w-hyperintensity on Spin Echo (SE) sequences, with a slice thickness of 4–5 mm, and compared DN SI to normal-appearing areas at the same level of the DN, such as pons or middle cerebellar peduncle. Similarly, studies analyzing GP SI changes have mainly used the thalamus as reference ROI. Although some Gd deposition is present also in these reference regions [45], this approach consistently proved that DN and GP SI increases with the increasing number of linear, but not macrocyclic, GBCA administrations. Some authors also used CSF as a reference ROI [17, 20]; however, GBCAs have been shown to pass, at least temporarily, into CSF [29, 46] and, as previously mentioned, CSF may actually represent a pathway to reach deep GM structures.

It is currently agreed that SE and Gradient Echo (GrE)-T1w sequences cannot be used interchangeably for evaluating SI, with some authors even preferring the latter for qualitative analysis [47]. Tanaka et al. [48] showed that post-contrast SE-T1 sequences could be used instead of unhenanced SE-T1, if the latter is unavailable. Furthermore, no study has compared the effect of different field strengths on these SI measurements [49]. However, serial measurements should obviously be performed using the same sequence and the same field strength, possibly on the same MR scanner.

To obviate some of the limitations related to qualitative parameters like SI, quantitative approaches for measuring GBCA-induced T1 shortening have been proposed. In 74 RR-MS patients exposed to different GBCA subtypes, Tedeschi et al. [50], using a validated relaxometry method [51, 52], assessed the R1 (1/T1) and R2* (1/T2*) relaxation rates, i.e., quantitative MRI metrics intrinsically related to tissue microstructure and not affected by the entangled contrasts of the SI images, or by acquisition-related confounding factors [53]. It was thus demonstrated that DN T1 shortening in patients exposed to Magnevist® is linked only to the number of previous GBCA administrations and not to R2*changes (and therefore possible iron build-up), nor to MS-related factors such as disease severity or duration. Using another relaxometry approach, other authors showed that global and regional T1 and T2 values correlate with the number and volume of prior Magnevist® injections in different gray matter structures [54].

Recently, Quantitative Susceptibility Mapping (QSM) has been used to evaluate DN susceptibility changes

associated with Gd retention, showing significantly higher DN susceptibility values in patients exposed to GBCA compared to subjects with no history of GBCA administration [55]. In this study, the 5 patients of the GBCA group who received only macrocyclic agents showed QSM values close to those of the non-GBCA group.

Further, other clinical conditions such as Fahr disease, pseudohypoparathiroidism, post-radiation therapy changes, Wilson Disease, Hepatic encephalopathy, etc., may cause T1-hyperintensity in deep gray matter [56], somewhat resembling Gd deposition (Fig. 2). Quantitative techniques such as QSM were shown useful for differentiating accumulation of paramagnetic metals from calcifications [57].

Finally, regardless of the imaging technique [58], other sources of variability should be taken into account. These include the time interval between GBCA administration and MRI acquisition, patient's characteristics such as age, type of disease, concurrent therapies [49], and the possible interactions between different classes of GBCA. For example, the DN T1w-hyperintensity due to multiple Magnevist® injection was apparently reduced when patients were subsequently given macrocyclic GBCAs, potentially indicating a washout effect or precipitation of Gd [19].

Gadolinium retention in the brain: histopathologic reports in humans and in animal models

Important information on tissue Gd deposition has also been provided by pathology studies. The first description of Gd retention in the brain of subjects without severe renal failure was a report on 30 biopsies and surgical resections of patients with brain tumors, and was firstly related to the loss of integrity of the BBB. This result provided indirect evidence of transmetallation and release of dechelated Gd in vivo, defined a different stability of GBCA (as Gd deposition was significantly higher in patients that received Omniscan® than in those exposed to Multihance®) and showed that Gd accumulation was related to the number of GBCA administrations [59]. Later, Gd deposition has been assessed using inductively coupled plasma mass spectrometry (ICP-MS) in post-mortem brain samples of subjects exposed to different linear GBCA [45, 60, 61].

In 13 autopsy subjects exposed in life to >4 administrations of Omniscan®, McDonald et al. detected 0.1–58.8 μg of Gd per gram of tissue in DN, GP, thalamus, and pons, with a significant correlation between dose and SI at MRI. Gd was deposited not only within the endothelial wall, but also in the neural tissue, confirming that Gd can pass through the BBB. Notably, no signs of neuronal damage in the involved brain tissue were observed [45].

In 5 autopsy subjects with an history of >2 administrations of Magnevist® and Omniscan®, a significant Gd concentration was observed in DN, GP, cerebellar white matter, frontal lobe cortex, and frontal lobe white matter, highest in DN and GP. Interestingly, no Gd deposition was found in the non-GBCA-exposed control group. Finally, no abnormal macroscopic changes were detected in the analyzed regions [60].

More recently, the autopsy specimens from 9 patients (five receiving 1–11 Prohance® injections, two

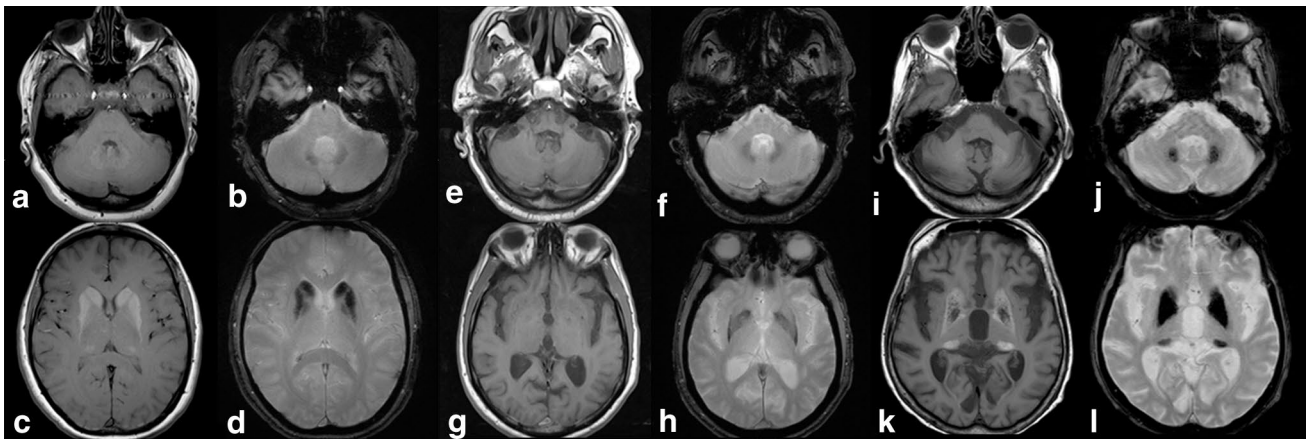

Fig. 2 Examples of increased T1-wighted signal intensity in the dentate nuclei due to different clinical conditions. Axial unenhanced SE-T1 (**a**, **c**, **e**, **g**, **i**, **k**) and GE-T2* (**b**, **d**, **f**, **h**, **j**, **l**) images at the level of dentate nuclei (*upper row*) and basal ganglia (*lower row*) in a patient with Fahr's syndrome (**a**–**d**), in a patient with neurodegeneration with brain iron accumulation (**e**–**h**), and in a patient with hypoparathyroidism (**i**–**l**), respectively. In all cases, the dentate nuclei display increased signal intensity (less prominent in e), associated with: T2*-w hypointense signal, due to symmetrical bilateral calcifications of the basal ganglia (**c**, **d**), T2*-w mild hypointense signal in the basal ganglia due to homogeneous iron deposition (**g**, **h**), and diffuse cerebral atrophy and strong signal reduction on T2*-w in the basal ganglia (**k**–**l**), with the T1 shortening effect dominating peripherally (**i**–**k**)

receiving 1–2 Gadovist® injections, one receiving 1 dose of Multihance®, and one receiving 10 Gadoxetate® injections) were studied by ICP-MS [61]. Variable Gd deposition was found in all subjects in DN, GP, putamen, caudate nucleus, white matter and pons, with higher levels in DN and GP. Comparing these data with those of Mc Donald et al. [45], Gd deposition after Prohance® was lower than after Omniscan®. However, the population sample for the other GBCA tested in this study was insufficient for a formal statistical comparison. Moreover, some confounding factors could not be excluded by the authors, thus limiting the conclusions that can be drawn.

Several animal studies have also been conducted to evaluate Gd deposition after repeated administration of different GBCA using MRI and/or pathology metrics.

In healthy rats, Robert et al. [62, 63] evaluated the SI in the deep cerebellar nuclei (DCN) and the concentration of Gd, through ICP-MS, after repeated administrations of different GBCA (Omniscan®, Multihance®, and Magnevist®) compared to Dotarem® and saline. Both studies indicate that multiple injections of linear GBCA were associated with progressive and significant T1w-hyperintensity in DCN (highest after Omniscan®), and with Gd deposition in the cerebellum, while no effects (either histologic or at MRI) were observed after Dotarem® or saline administration.

In a similar rat model, Jost et al. [29] compared Omniscan®, Multihance® and Magnevist® (linear) with Dotarem® or Gadovist® (macrocyclic) and with saline. Rats that received macrocyclic GBCAs did not show an increased SI in the DCN or GP. In contrast, DCN/Pons SI ratio was increased after the administration of linear GBCAs, most pronounced after Omniscan®, followed by Multihance®.

Further studies with ICP-MS have shown that, by increasing the Gd load from linear GBCA (by either incrementing the dose or reducing the renal clearance), Gd deposition is present not only in the DCN, but also in cerebral cortex, subcortical brain, brainstem, olfactory bulbs and pons, [40, 62, 64]. However, it was recently shown that, even after 12 mmol/kg of Omniscan®, no histopathologic changes were observed in the rat brain, and only 0.00011% of the injected dose was retained at 20 weeks [65].

Gadolinium retention beyond the brain

Bone

Bone has long been known to be a preferential site of Gd deposition [66], and likely serves as a reservoir of Gd in the body [67]. Nevertheless, that was not common knowledge in the radiological community, likely because of the lack of association with signal abnormalities at MRI. It has been estimated that approximately 0.25–1% of the injected Gd may be released from the contrast agent and deposited in the bones, even in patients with normal renal function [68].

In particular, in the resected femoral heads of patients who underwent total hip arthroplasty 3–8 days after CE-MRI with Omniscan® or ProHance®, the amount of Gd deposited in bone was 2.5–4 times higher in subjects who received the former GBCA [69, 70]. This difference was not replicated in another study, where resected femoral head bone samples up to 8 years after Omniscan® or ProHance® exposure showed high concentrations of Gd, especially in the trabecular bone [68]. Recently, high levels of bone Gd deposition after macrocyclic GBCA administration were measured by ICP-MS in few decedents with a normal GFR. Therefore, bone measures of Gd accumulation have been proposed as an indirect method to indicate approximate levels of Gd in brain [61].

Skin and other sites

Most of the information about Gd deposition in the skin comes from studies in patients with NSF, who showed increased Gd content both in affected and unaffected skin [71–73]. The first evidence of NSF was reported in 2006, showing skin fibrosis resulting from abnormal proliferation of fibroblasts and collagen in patients with severe renal impairment after GBCA administration [74]. It soon became clear that, in patients with renal failure, the highest risk of NSF was associated with previous administration of linear GBCA with an incomplete ring [75]. In an autopsy case of a patient who died of NSF, deposition of insoluble Gd-phosphate was observed in skin, liver, lungs, intestinal wall, kidney, skeletal muscles and cerebellum [76]. However, while several studies suggest that impaired Gd clearance leads to tissue accumulation of dissociated Gd and promotes NSF development, only a tiny minority of patients with severe renal disease exposed to linear GBCA developed NSF [3].

More relevant for our purposes is the evidence of detectable Gd concentration also in the skin of subjects with normal GFR exposed to GBCA [73]. In a brain tumor patient with normal renal function who received 61 injections of mostly linear GBCA, arm and leg biopsies of deep skin layers were performed because of severe generalized joint contractures. High levels of Gd were deposited in the skin of this subject, associated with signs of inflammation (as depicted by an increased numbers of fibrocytes or macrophages, as well as increased CD34 immuno-reactivity in subcutaneous adipose tissue), in the absence of local skin alterations [77].

Using ICP-MS, Murata et al. detected a variable amount of Gd deposition in the skin (as well as brain and bone) in a series of autopsied patients with normal renal

function who had received macrocyclic or linear GBCA. Gd concentration was lower in skin tissue after Prohance® than after Multihance® [61]. Therefore, in contrast with previous knowledge [78], even in patients with normal renal function, in vivo clinical exposure to GBCA results in Gd accumulation into different body tissues such as skin, bone matrix or brain. Moreover, Gd retention increases with repeated GBCA exposure. Data from rat studies, which have long shown Gd accumulation in skin, liver, spleen, bone and brain [79, 80], recently confirmed the marked difference in tissue deposition between linear and macrocyclic GBCA [81]. However, the final form in which Gd is deposited in the tissues is still uncertain and little is known about the levels of Gd required to induce tissue structural changes and to achieve clinical significance in humans [47].

Clinical concerns from gadolinium retention

After the almost complete disappearance of NSF by limiting or avoiding the use of GBCA in subjects with advanced renal failure and employing more stable GBCAs, the only unconfounded clinical events associated with GBCA administration were sporadic allergic reactions [3].

Following the reports of Gd retention in the brain in 2014, a variety of symptoms arising shortly after the administration of GBCA were described in patients with normal renal function. In some of these patients, the persistence of Gd was demonstrated by its elevated concentrations in urine, hair, or in the saphena vein [82, 83]. This presumed disease process, observed in subjects with normal (or borderline) renal function who develop symptoms unexplained by other preexistent or subsequent diseases, has been named "Gadolinium Deposition Disease" (GDD) [83, 84].

Alleged GDD symptoms include tightness or excruciating pain of the arms and legs (like sharp pins and needles, cutting, or burning), typically in a distal distribution (like being fitted with extremely tight "glove-and-sock"), but also in the central torso or generalized in location. Bone pain and persistent headache with clouded mentation ("brain fog") were also commonly reported [83, 84]. These symptoms usually appear from hours up to 2 months after the last CE-MRI (mostly within 1 month), with persistent pain in the extremities [83]. However, it should be noted that the clinical picture of the presumed Gd toxicity in these subjects was collected by one single research center, using an online anonymous survey where 42 patients self-reported their symptoms, without a control group. Thus, this approach is heavily exposed to selection bias, as also stated by the authors themselves [83, 85].

In some patients, subcutaneous soft-tissue thickening ("Gadolinium-associated plaques") may be observed. It appears spongy or rubbery, in contrast with the stiffness and redness typical of NSF lesions. Moreover, tendons and ligaments in a comparable distribution may also be thickened and painful [84]. In 2 patients without NSF exposed to Omniscan®, sclerotic bodies (eosinophilic, collagenous, round or ovoid bodies, thought to be pathognomonic for NSF) were found at histopathologic examination of the skin [86].

The symptoms described might be considered as a toxic effect of Gd, resembling the development of NSF. According to a Team of Patient Advocates, which timely entered in the field, "the reported physical symptoms of Gd deposition disease are similar but not identical, and lesser in severity, to those observed in NSF" [84, 87]. However, the causal relationship between GBCA and chronic effects is not fully established, and only hypothesized [84, 88].

The reason why only a small percentage of patients develop symptoms after GBCA administration is unclear, as with NSF. An hypothesis is that less stable GBCA are more likely associated with symptoms, similarly to NSF, with other host factors, such as genetic susceptibility and/or adaptive immune response, likely playing a relevant role in determining the development of GDD [84]. However, these clinical findings were surprisingly reported even after one single administration of all GBCA, excluding Dotarem® [82, 83]. Thus, a well-conducted, prospective evaluation of the real clinical incidence and pathogenesis of the presumed GDD is strongly warranted, especially due to the high impact of this topic not only in the scientific community, but also in non-specialized media.

Gd neurotoxicity has been rarely described in early cases of presumed Gd-induced encephalopathy, in patients with renal dysfunction and other significant comorbidities [89–92]. It is actually unknown if the Gd retention in the brain has a clinical correlate, or leads to adverse neurological effects. So far, no significant association between Gd exposure and the development of Parkinsonism or other movement disorders has been demonstrated [93, 94]. None of the imaging studies on Gd-induced T1w shortening reported neurological symptoms related to GBCA administration, and no signs of tissue damage were observed in human or animal pathology studies. However, due to the description of nonspecific symptoms, such as pain or cognitive changes, after Gd exposure [47], further research is warranted to assess the long-term impact on public health and safety of deposition of Gd in the brain.

The US Food and Drug Administration (FDA) and the National Institutes of Health (NIH) have recommended careful consideration about the indication of GBCA, by "limiting GBCA use to clinical circumstances in which the additional information provided by the contrast is

necessary" [95], and suggested the preferential use of macrocyclic agents [96]. In January 2017, the European Medicines Agency (EMA) has announced that its Pharmacovigilance Risk Assessment Committee (PRAC) will continue to evaluate the risk of Gd deposition, and that, once PRAC's recommendations will be issued, the agency's Committee for Medicinal Products for Human Use will adopt a definite position. The European Commission will then complete the review process by adopting a legally binding decision applicable in all European Union member states [97]. Regarding the presumed GDD, the Drug Safety Communication of the US-FDA declared that, despite patient's self-reports, to date there are no discernable clinical features reasonably linked to GBCA administration [95].

Thus, several clinical questions remain open [98]: does Gd retention affect the function of the tissues where it is deposited and lead to clinical consequences? Does GDD exist and, eventually, is it dose- or GBCA- dependent? Is the Gd deposition in the brain one manifestation of a more complex Gd deposition syndrome that may also encompass NSF? What is the role of immune system components and genetics in determining different symptoms?

For all these reasons, a systematic scientific approach is necessary to this delicate matter, which has manifold medical and legal implications [93]. Until additional information is obtained, radiologists and clinicians should work together to monitor the development of NSF-like disease or toxicity symptoms allegedly related to GBCA administration in patients with normal renal function, without however scaremongering patients undergoing a CE-MRI scan. In such cases, a 24-h urine testing may be useful for confirming the presence of Gd > 30 days after the most recent GBCA administration [84].

Conclusions: what we can do

Some final considerations and practical suggestions may be summarized from this review of the available literature about Gd retention, while waiting for official guidelines and consensus statements developed by major national/international scientific radiological societies or from an international strategy of cooperation, such as the recently established International Gadolinium Retention Evaluation Consortium, that involves several worldwide scientists [98].

First, in patients referred for a CE-MRI, we should try to obtain all information on possible previous GBCA administrations and evaluate the need of contrast administration even more critically than ever, especially in pediatric cases. In this respect, the idea of creating and updating an individual GBCA administration passport is warranted [98].

Second, the preferential use of macrocyclic GBCAs, due to their higher stability over the linear types, is recommended. This is especially true in children and in subjects for whom multiple studies are anticipated (e.g., patients with Crohn disease or MS) [84]. However, if macrocyclic GBCAs are unavailable and a CE-MRI is clinically indicated, we believe that linear GBCA may be administered, since all GBCAs provide essential radiological information with exceedingly positive risk/benefit ratio for the diagnostic challenge of individual patients.

Third, the presence of T1w hyperintensity in the DN (or in any other brain region) should always be described in our reports, and may prompt careful questioning of the patient about the history of prior Gd administration. However, interpretation errors should be avoided [99], and other possible causes of spontaneous T1w hyperintensity should always be considered (Fig. 2).

Fourth, it should be borne in our mind that, despite some alleged symptoms (as discussed above), at the time of this writing there is no known disease associated with Gd deposition in the brain, and several millions of patients with normal renal function have received GBCA without incurring in any related health problems. Therefore, we should not deny the patients a sure benefit in fear of a possible harm.

As radiologists we are given a delicate role in providing our patients balanced information on a largely unknown situation. A truly informed consent must be obtained from the patient or parent before GBCA administration, clearly explaining them the potential risk that Gd may be deposited in their body, with still unknown (but possibly unremarkable) clinical consequences. On the other hand, we should make clear that the diagnostic accuracy of many MR exams might be reduced if GBCA is not administered, with direct effects on the clinical management of the patients.

Compliance with ethical standards

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Conflict of interest All authors (Enrico Tedeschi, Ferdinando Caranci, Flavio Giordano, Valentina Angelini, Sirio Cocozza and Arturo Brunetti) declare that they have no conflict of interest.

Informed consent The MRI scans shown in the figures were retrospectively selected among MRI studies previously performed according to clinical indications, with informed consent obtained from all individual participants.

Ethical statements This article does not contain any studies with human participants or animals performed by any of the authors.

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