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Review

Toxicity associated with gadolinium-based contrast-enhanced examinations

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Abstract: This article reports known and emerging adverse health effects associated with the administration of gadolinium-based contrast agents. It focuses on the issue of the incomplete excretion of these drugs leading to the deposition of gadolinium in the tissues of the patients. The evidence of deposition is reviewed. The analysis presents gaps in our knowledge but also suggests neglected or still poorly considered parameters to possibly explain discrepancies among studies (e.g. off-label use; rate of administration; gadolinium concentration in the pharmaceutical formulation, cumulative metal toxicity). The article also presents a critical assessment of some aspects reported in the literature as well as future needs. Potential biases in the investigation and evaluation of the health/clinical implications associated with gadolinium deposition are pointed out. The analysis emphasizes that the vast majority of the clinical studies conducted up to date on gadolinium-based contrast agents were designed to assess acute toxicity and diagnostic efficacy of the agents, not to identify long-term health effects.

Keywords: gadolinium; magnetic resonance imaging; gadolinium-based contrast agents; adverse events; toxicity; gadolinium retention; gadolinium deposition

1. Introduction

Gadolinium-based contrast agents (GBCAs) are soluble metal-ligand complexes of gadolinium ion Gd^{3+}. Contrast agents fall into the definition of drugs as a tool for making a medical diagnosis [1]. GBCAs have been developed to provide additional information on pathological tissue: they increase the sensitivity and specificity of detecting and evaluating various pathologies [2], of significant relevance for discriminating cancer cells [3–6]. GBCAs are exclusively approved for use in

conjunction with a diagnostic procedure [7]. GBCAs have peculiar physical requirements as relaxation agents [3,8] and stringent biological demands for non-toxicity as pharmaceuticals and medical diagnostic tools [3]. Chelation by organic ligands is designed to protect the tissue from the interaction with Gd^{3+} preventing its cellular uptake before fast excretion in the urine [9–11].

Gadolinium (Gd) is the metal sitting in the middle of the lanthanide series. Gd^{3+} is well known to be toxic for living beings. Uncountable interferences of Gd^{3+} in biological systems both in humans, animals, and plants are known since tens of years [12]. Toxicity of Gd^{3+} in biological systems is largely caused by its ability in mimicking divalent endogenous cations, above all calcium ions (Ca^{2+}). It occurs not just for its ionic radius close to that of Ca^{2+} but also similar coordination number, donor atom preferences, and binding behaviour [12]. The toxic potential of Gd^{3+} when substituting cations such as magnesium, zinc, and iron should not be neglected as well, particularly for the role of these ions as co-enzymes in several biochemical processes in mammals [12]. Nevertheless, Gd^{3+} has unique physico-chemical properties that make it the best probe to date for contrast enhanced (CE) magnetic resonance (MR) investigations for diagnostic purposes [13]. Thus, detoxification of Gd^{3+} by strong organic chelators is essential for in vivo administration at dose relevant to contrast enhancement for diagnostic value [10].

Contrast agents can be classified depending on the nature of the molecular structure of the ligand: linear (i.e., open-chain molecule) or macrocyclic (i.e., cyclic ligand) and ionic (i.e., dissociation into charged particles occurs in solution) or non-ionic [10]. Different chelating molecules have been developed and introduced in clinical practice since the eighties [11]. The pharmaceutical chelate determines the pharmaco-kinetic of the agent and *in vivo* distribution [3,11].

2. Known adverse drug reactions of GBCAs

Despite the excellent safety profiles of GBCA respect to other contrast agents (e.g., iodinated contrast agents), adverse drug reactions (ADRs) occur. The rate of known acute ADRs associated with gadolinium-based contrast agent (GBCA) administration has been estimated to range from 0.07% to 2.4% [14]. The primary sorting is between those anaphylactic [15–18] and non-anaphylactic in origin [19] and renal and non-renal [10,20–26].

2.1. Non-renal acute and severe ADRs

Anaphylactic reactions are rare adverse drug reactions (ADRs) [16]. Few reports of anaphylactic ADRs of GBCAs have been published [17,18]. Anaphylactic reactions are difficult to predict [27] unless a previous reaction to the same agent has already occurred [18]. They are usually fast up to immediate and can lead up to very fast fatal outcomes [17,18].

2.2. Acute mild ADRs

Acute local (ADRs) have a much more favourable prognosis. Most common acute mild ADRs are emesis, nausea, headaches or local reactions at the site of injection. The last ones comprise local necrosis, edema, and inflammation [28] mainly due to contrast extravasation into tissues [10,20,21], erythema, swelling, pain at and proximal to that site: they typically occur early, within few days after administration, they peak and resolve over some days [28]. Delayed-onset cases of ADRs are also

known. Varied gastrointestinal, neurological, respiratory, dermatological, cardiovascular, and more generalized non-specific adverse reactions have been reported [28].

2.3. Nephrogenic systemic fibrosis

The main known acute renal adverse reaction of GBCAs is nephrogenic systemic fibrosis (NSF), yet cases with delayed onset had been reported [29–31]. NSF is a painful fibrosing disorder associated with impaired excretion of GBCAs in subjects with kidney diseases. It is chronic, often progressive, and even life-threatening [32–35]. Historically, symptoms associated with inefficient excretion of GBCAs were initially recognized in patients with renal impairment, described as a unique cutaneous fibrosis disorder named nephrogenic fibrosing dermopathy (NFD) [36]. The first case was diagnosed in 1997 and published in 2000 [37]. It was characterized by cutaneous changes, "indurated plaques and papules" mainly on the extremities, "thickening and hardening of the skin associated with brawny hyperpigmentation". A unique histopathological finding emerged [36]. When extra-cutaneous fibrosis was observed, it led to the definition of a new clinical condition termed NSF [32,36]. NSF is early characterized by progressive skin thickening, tethering, pain, swelling and skin lesions often pruritic [32,38]. Patients often develop joint stiffness and contractures, muscle weakness and deep bone pain [38]. Epidermal atrophy, follicular dimpling (peau d'orange), hair loss, mild to moderate edema are also reported often later in the course [32,39]. Radiographic images show abnormalities other than skin alterations in NSF confirmed biopsy patients-but described as non-specific alterations [38,40]. Acute kidney injury, chronic kidney diseases, end-stage renal failure, and glomerular filtration rate (GFR) or estimated GFR below 30 ml/ min/ 1.73 m^2 are considered as the main risk factors [35,41]. Additional risk factors include "pro-inflammatory events" at time of GBCAs administration (including surgery), epoetin use, acidosis, hyperphosphatemia [39], liver dysfunction [42,43], high doses and multiple administrations [34,39,44]. Yet, NSF cases with biopsy confirmation have been reported in subjects who received a single dose [38,41].

Still the pathophysiology of NSF is not fully understood, and it lacks a cure. The presence of gadolinium seemed to drive fibrosis in the context of renal dysfunction, thus NSF has been proposed to be renamed "gadolinium-associated systemic fibrosis" (GASF) to better reflect the pathogenesis of the disease, being the term "nephrogenic" misleading [45,46].

The stability of Gd^{3+}-complexes has been correlated with the likelihood of releasing gadolinium ions in vivo [47] and inducing fibrosis [32]. The linear agents have been categorized as more likely to predispose to the development of NSF [32]. The pharmaceutical formulation of the agents has been also considered, and the lesser quantity of added free ligand has been associated with higher incidence of NSF [48]. Conversely, the excess free ligand (or sodium or calcium salt complexes) enhances the probability of chelating endogenous cations and thus the probability of leading to retention of pharmaceutical chelates complexed with ions other than Gd^{3+} [48].

The manifestation of NFS opened several questions on the real in vivo safety and stability of GBCAs. Concern on gadolinium retention in humans openly emerged for the first time and led to regulatory updates (i.e., first call for box warnings in 2007 [49]). Revisions of the procedure guidelines, restriction of their use in patients with renal diseases, and best practice recommendations [50,51] highly decreased the incidence of NSF [52,53]. Guidelines recommend careful evaluation of each case, balancing benefits, risks, and disadvantages. Whilst anaphylactic reactions are very rare and often difficult to be prevented, judicious approach to the administration of GBCAs in patients with

underlying kidney diseases appears the most effective strategy to prevent NSF [35].

3. Gadolinium deposition

3.1. Gadolinium deposition within brain

Novel toxicity issues were raised when the evidence of incomplete excretion was reported in subjects with normal renal function. Gadolinium deposition has been early investigated in biopsies of brain tumours by Xia and colleagues in 2010 [54]. They found insoluble deposit containing gadolinium associated with phosphorus and calcium, particularly in specimens from patients who received multiple administrations of GBCAs. In 2013, deposits were measured in autoptic brain samples by Kanda et al. [55]. Abnormal hyperintensity in non-enhanced MRI images was detected in the dentate nucleus of the cerebellum and in the globus pallidus and were associated with gadolinium deposits confirmed by analysis of autoptic brain specimens. In 2015, McDonald et al. reported similar results in several brain structures, suggesting widespread accumulation of gadolinium in the brain parenchyma and correlation between administered dose and signal intensity enhancement [56]. Since 2015, a great number of studies has been performed to assess gadolinium deposition [57–59]. The bulk of literature data reported gadolinium deposition as associated with the administration of linear agents both in humans (adult and paediatric patients) [60–73] and in animals [74–79]. Imaging studies with macrocyclic agents often have not shown marked abnormal hyperintensity in specific brain areas and this evidence led to state the absence of gadolinium deposition [80–85]. Nevertheless, evidence of deposition associated with the administration of macrocyclic agents exists [86–91]. Brain deposits have been measured even in the absence of hyperintensity [92].

In summary, deposition associated with linear agents is a tenet, whilst deposition associated with macrocyclic agents remains more debated. Yet, even a single dose of a macrocyclic agent has recently caused detectable gadolinium deposits in the human brain tissues measured in autoptic samples [86].

3.2. Gadolinium deposition within bone and hair

Major attention on gadolinium deposition in humans has been paid to the brain, despite initial evidence of deposition was earlier reported in the bone. Gadolinium deposits in femoral heads of patients who underwent total hip arthroplasty were investigated *ex vivo* by Gibby et al. [93] in 2004 and by White et al. in 2006 [94]. Few years later, a similar cohort of patients was the object of investigation by Darrah and co-workers [95], who measured high gadolinium levels years after the exposure to GBCAs. In 2016, Murata and colleagues [96] measured gadolinium deposits both in bone and brain tissues of patients receiving GBCAs. Albeit the number of administrations and time distances from administrations and analysis were highly variable among cases considered, bone median levels were significantly (i.e., up to 23 times) higher than the already abnormal brain levels. In 2018, Lord et al. [97] measured deposition of gadolinium in the bone *in vivo* in apparently healthy volunteers and demonstrated that gadolinium can be retained and detected in bone after a single dose. More recently, Turyanskaya and colleagues [98] detected and mapped gadolinium accumulation in a bone biopsy of a male patient with idiopathic osteoporosis: Gadolinium distribution occurred in cortical bone tissue and correlated with other detected elements, as calcium and zinc. Gadolinium

deposition in the skeleton has the potential for systemic adverse effects impacting on body homoeostasis [95]. Like other lanthanides, the biological half-life of gadolinium in the bone has been reported for almost two decades, depending on animal species under consideration [99]. Delayed mobilization of gadolinium from bone stores during the process of bone remodelling carries the possibility of delayed and long-term adverse effects [95]. Methods of analysis based on radiation physics *in vivo* might be helpful to investigate the real incidence and prevalence of gadolinium deposition, of particular interest concerning the bone [100]. Yet, hair and nail analysis might be even a better tool for accessing metal deposition, because fully non-invasive. Hasegawa et al. [101] have recently published evidence of gadolinium in hair using laser ablation inductively coupled plasma mass spectrometry. The study found significant correlation between hair and brain gadolinium concentrations, especially in white matter and dentate nucleus among decedents who received GBCAs. Despite the small number of subjects involved in the pilot study, the results are very promising. Hair analysis might be a reliable method to noninvasively sampling, quantifying, and monitoring gadolinium (and other lanthanides) *in vivo* in humans. The technique is also relevant to investigate the time dynamics of deposition and delayed wash out. Considering that the concentrations of metals in hair are usually order of magnitude higher than in the blood and urine [101], it can be a very attractive tool for buoying gadolinium deposition and associated possible chronic and sub-chronic toxicity, also abating false-negative results from delayed blood or urine examinations. Fingernail analysis has also been used to demonstrate gadolinium intoxication [102].

3.3. Market restrictions and possible unrecognised adverse health effects

In 2015 U.S. Food and Drug Administration (FDA) published the first drug safety communication on gadolinium deposition, yet without recognizing any associated disease [103]. Regulatory actions by the European Medicines Agency (EMA) acknowledged the evidence of deposition associated with linear agents in 2017. EMA embraced a precautionary position in patient's safeguard: Restrictions and suspensions of marketing authorizations have been implemented in Europe [104]. EMA suspended the use of most linear agents [104]. But only few other regulatory authorities followed a similar approach, mainly in the Middle East (i.e.; United Arab Emirates, Jordan and Kingdom of Saudi Arabia) [105]. Variably updating of package insert and recommendations have been required in the rest of the world [105]. The Pharmaceuticals and Medical Devices Agency restricted linear agents to second line agents in Japan and asked for revision of the precaution indications [106,107]. Conversely, all the nine GBCAs still maintain the marketing authorization in the rest of the world [105], and this position reflects that of the U.S. Food and Drug Administration [7,105] and the American College of Radiology [108]. In 2017, they recognized the occurrence of deposits in humans, but they found no evidence of harm for patients [108]. Notwithstanding, new class warning have/should have been introduced updating the prescribing information, requirements, and prescriber/dispenser actions asking for advising patients that "*gadolinium is retained for months or years in brain, bone, skin, and other organs in patients with normal renal function*"[109]. And "*the clinical consequences of retention are unknown*" [109]. This warning update also pro-actively disentangles industrial producers and physicians from litigations that are growing in the U.S. [110]. In 2016, Semelka et al. published a collection of cases reporting symptoms following GBCA administration in patients with normal renal function [111]. It was the first hint of a still unrecognised clinical condition of a possible systemic gadolinium toxicity. The

term *gadolinium storage condition* was initially coined to define the condition with no excretion and no symptoms, where the gadolinium is supposed to lie "primarily inert within the body". A symptomatic condition where gadolinium is not inert was termed *gadolinium deposition disease* by Semelka and colleagues, thus highlighting a possible new clinical entity [112]. A survey of patients with chronic symptoms following GBCA administration was published the same year and data from FDA Adverse Reporting Symptoms [113]: The self-reported symptoms spanned from musculo-skeletal ones, such as bone and joint pain, joint contracture, burning and sharp pain in the torso, legs, and arms to fatigue, flu-like aches, paraesthesia, headaches, cloud mentation, diminished memory and skin changes. Gadolinium containing deposits were also variably reported in urine, hair, and skin of the patients in the survey [114,115]. The same year, Roberts et al. reported severe joint contracture of unknown aetiology in a brain cancer patient who had gadolinium deposits in the skin and showed marked signs of gadolinium deposition in the cerebellum after a large number of GBCAs administrations [116].

High signal intensity in the DN and GP on unenhanced T1-weighted MR images was reported also in patients with impaired renal function by Barbieri et al. [117]. And of note, the authors reported that all three patients object of the study suffered from "transient sign of neurological disorders of undetermined cause" [117]. Similar unexplained clinical observations have been reported by Swaminathan [118], who referred to "several patients with normal renal function and significant residual gadolinium who manifest new-onset unexplained extremity pain (neuralgic type) and stiffness without any definite evidence of NSF after exposure to GBCAs". In 2020, it has been published a case reporting signs of gadolinium deposition in the brain and a causal role for gadolinium in the aetiology of the symptoms experienced by the patient after multiple administrations of a macrocyclic contrast agent in the contest of normal renal function [91].

3.4. Investigating the mechanisms of gadolinium deposition

The biophysical mechanisms that govern deposition and associated toxicity are not fully understood. The role of short-term dechelation of linear Gd^{3+}-complexes might be only the simplest part of the toxicity, since retention of the intact complexes has been reported [79,116,119–121]. Receptor-mediated endocytosis of chelated gadolinium has been also observed [122]. Intact complexes carry toxicity issues not only due to the possible delayed mobilization of gadolinium, but also by their-own, without dechelation to occur. Early in the 1980s, Lauffer reported that chelate toxicity includes alteration of membrane potentials, enzyme inhibition, or nonspecific protein conformational effects [3]. A recent study by Kartamihardja et al. [121] in mice demonstrated that gadolinium may be distributed throughout the brain tissue in chelated form, possibly via the choroid plexus. Bonding of intact complexes to macromolecules has been also demonstrated and deposits have been variably found in rats in different forms including, in addition to intact complexes, soluble small molecules, soluble macromolecules, and insoluble species [123]. Gadolinium accumulation within the cerebro-spinal fluid has been reported in humans, even in the setting of normal renal function and without blood-brain-barrier dysfunction [124]. It has been also recently proved that intact complexes can be internalized by leukocytes and erythrocytes. Despite the large majority of the complexes remaining in plasma, GBCAs seem to be able to cross the membrane of blood cells and be internalized by diffusion or, possibly, by pinocytosis [119]. Other studies by Di Gregorio and colleagues in animal models support the view that the majority of gadolinium retained in the brain arises

from intact complexes that have extravasated immediately after the intravenous administration [120]. The internalization of more stable complexes might be of long-term impact by delayed dissociation.

It is still unclear which gadolinium-containing species (Gd-species) is producing T1-shortening associated with gadolinium deposit in imaging data [125]. The term "species" and "speciation" refer to the chemical form of the deposits containing gadolinium [126]. It has been hypothesized that insoluble gadolinium-species are not responsible for T1-signal enhancement [74]. Retained gadolinium in the brain tissue may be bound to organic molecules, including proteins [121]. Both soluble and insoluble species have been detected [74,116], but a speciation analysis of the deposits is often absent or it is intrinsically hampered by the low concentration of deposits, methods of analysis or sample treatment [120,127] (e.g.; nitric acid digestion [95] or wash out of soluble entities [75]). Also, a detection limit exists not only in imaging analysis but also in quantification studies and it may vary from different techniques and instruments: In a recent study performed on a large animal model it has been reported that the quantitative analysis had a limit of 5.7 ng gadolinium/g tissue, while it was reported that gadolinium becomes visible in MRI if a threshold of approximately 1 μg gadolinium/g of tissue is exceeded [76]. It has been speculated that different degrees of angiogenesis and potential microleaks may result in visually undetectable gadolinium on conventional T1-weighted MRI due to low gadolinium concentration [128]. Imaging studies reporting negative results may confirm lack of signal enhancement, but not lack of gadolinium deposits. The case study by Roberts and colleagues quintessentially lends support to the relevance of this situation: gadolinium deposits have been found in autoptic brain samples in the absence of any hyperintense signal in magnetic resonance images [92]. Similarly, Kiviniemi and colleagues detected gadolinium deposits in glioma specimens and in adjacent normal brain tissue that showed no evident contrast enhancement on T1-weighted MR images [128]. The hypothesis of a widespread deposition in the brain parenchyma has been supported by previous evidence on human brain autoptic samples [56,129]. The role of tissue density might be also important to produce a detectable hyperintense signal from deposits and it might explain the reason why hyperintensity in the cerebellum has been earlier noted. The cerebellum has high cell density [130] and it is a major repository of metals [131]. The dentate nucleus is particularly rich in copper localized to the periphery, whilst iron and zinc are abundant centrally [131].

3.5. Delayed manifestation of gadolinium toxicity: the lack of evidence and the evidence of absence

The most urgent gap to fill concerns the existence of health effects associated with gadolinium deposition. A definitive consensus still lacks and international research efforts are ongoing [125]. To the best of our knowledge, a single epidemiological retrospective imaging study in healthy volunteers who underwent whole-body MRI have been published. The study, supported by the industrial producer of the agent, was published in 2017 based on data ranging from 2008 to 2012 [132]. It failed to find a difference in relative signal intensities of selected brain structures 5 years after a single administration of a 1.5-fold the minimal standard dose of the macrocyclic gadolinium complex gadobutrol; i.e., 0.15 mmol/kg (the concentration of the gadolinium is not reported in the paper but in the past gadobutrol was available at two different concentrations, 1M or 0.5 M concentration [133]). It can be concluded that the administration of the above mentioned dose and agent in healthy subjects does not cause hyperintensity in specific brain regions 5 years after administration.

The main argument of those who deny harm associated with gadolinium deposition is the lack

of clinical evidence. But at least two considerations can be done against this belief and to support the thesis that long-term studies are needed to draw final conclusions:

(i) the most of the imaging studies designed to investigate gadolinium deposition aimed to elucidate an imaging finding, and not its clinical significance. These studies investigated the existence of abnormal hyperintensity in the brain, not its clinical significance, as explicitly declared in the aims of the study [67];

(ii) the majority of the studies conducted up to date on GBCAs were designed to access acute toxicity and to investigate diagnostic efficacy of the agents, not to identify long-term health effects. Indeed they had short time follow-ups. The investigation of the onset of adverse reactions occured within few days after the administration of GBCAs. This period of time allow to assess the acute toxicity. Examples among the recent ones are: 72 hours after GBCA administration in the phase III study by Gutierrez et al. [134]; 24 ± 4 hours after GBCA administration in the phase III study by Kuwatsuru et al. [135]; 24 hours after GBCA administration in the study by Liang et al. [136]; time window not reported, but clinical outcomes were limited to renal function before and after administration and occurrence of contrast-induced-nephropathy in the study by Naito et al. [137]; time window not reported in the study by Semelka et al., but clinical outcomes were acute, visually apparent adverse events [138]; 72 hours after GBCA administration in the study by Tanaka et al. [139]; time window not reported in the phase III study by Zech et al. [140]. Long-term adverse effects are intrinsically overlooked if the study follow-up is restricted to a few days. The issue of chronic toxicity has been mainly evaded, despite (i) more than 30 years of clinical use and despite (ii) the evidence of gadolinium deposition in bone, liver, kidney of rodents after exposure to linear agents has been known since the 1990s [128,141]. However, the risk of potential accumulation of gadolinium in humans had been taken into a possible scenario, but poorly considered at that time as believed "unlikely [GBCAs] to be administered repeatedly in patients" [142]. But, repeated administrations have become a reality in several cohorts of patients, like long-term cancer survival, multiple sclerosis patients or subjects with chronic pathologies. Concerns were also explicitly pointed out by Shellock and Kanal in 1999 regarding the accumulation of the MR imaging contrast agents after multiple doses administered to patients: Despite they pointed out the lack of data regarding the safety of long-term cumulative exposure to low doses of free gadolinium ion and the need of further investigations, the hypothesis of "a clinical limitation to the number of times a patient can be safely scanned with gadolinium-based contrast agents" was elicited [28]. Some studies in animal models and one in pregnant women showed some possibilities of long-term gadolinium toxicity. Khairinisa et al. examined the effects of perinatal exposure to GBCAs on the behaviour of adulthood offspring and showed that gadolinium can be transferred to pups and was retained in their brain during postnatal development. This occurrence may lead to impaired brain development and affect motor coordination, memory task, tactile sensitivity and cause anxiety-like behaviour [143]. Ray et al. investigated toxicity associated with GBCAs in humans and found that gadolinium at any time during pregnancy was associated with an increased risk of a broad set of rheumatologic, inflammatory, or infiltrative skin conditions and for stillbirth or neonatal death [144]. Investigations in animal models by Runge et al. reported sub-chronic toxicity of the GBCAs, i.e. the potential for premature loss of ovarian function [145].

More recently, gadolinium deposits have been reported in the spinal cord and peripheral nerves in rats exposed to multiple administrations of linear and macrocyclic contrast agents [146]. No hippocampal neurogenesis or altered spatial working memory performance have been observed from

animal tests, but heat and mechanical hyperalgesia has been associated with the linear agents. The authors hypothesize the sensitization of spinal cord nociceptive neurons and that gadolinium in the spinal cord and peripheral nerves might contribute to sensory symptoms and burning pain in the torso and extremities described by some patients [146].

4. Remarks on known and still poorly considered parameters playing a role in deposition

Reduced renal function and liability to dechelation and transmetallation have been recognized as the main responsible for gadolinium deposition in the tissues. Yet, deposition of intact complexes occurs. The role of transporter proteins and bounding to macromolecules has been investigated and showed that GBCAs are able to penetrate a series of brain barriers [121]. Repeated administrations increase the risk of deposition and several studies showed that a dose-dependent relationship exists between the number of GBCA administrations and the amount of gadolinium deposits [56,89,90,62,85]. Inflammation has been shown to facilitate gadolinium retention into brain tissue [147]. Animal studies investigating the involvement of the glymphatic system activity suggested a role played by anaesthesia, sleep, and morning administration to facilitate the glymphatic clearance in rat brain [123].

Table 1. Parameters that play or might play a role in gadolinium retention/toxicity.

Types of parameters	Parameters and conditions
Known [9,95]	• Thermodynamic and kinetic stability of the agent • availability of the potential transmetallation partners • administered dose (single high level exposure)
to further/better evaluate [123,126,147]	• cumulative dose • low-level cumulative storage • distance among subsequent administrations • medications (eg; epoetin, glucocorticosteroids,...) • inflammation, pro-inflammatory events, acidosis, hyperphosphatemia, and liver dysfunction • co-exposure to high intensity static magnetic field, time-varying magnetic field gradients, and radio frequencies during examinations • role of anaesthesia • dose conversion from animals to humans • protein binding • intact pharmaceutical complexes (i.e.; without dechelation to occur) • metabolic conditions (e.g.; diabetes, fasting, ...)
Suggested to investigate	• rate of administration • gadolinium concentration in the pharmaceutical formulation • gender (e.g.: relevance for dosing, susceptibility to toxicity, role of hormones) • intra-individual analysis • implants and prostheses • rare earths present as impurities in the agents

Here, other parameters that might play a role are suggested to be considered in future studies:

i. The rate of administration and the concentration of gadolinium in the pharmaceutical formulation of the agents.
ii. The time interval among subsequent administrations and the cumulative dose.
iii. The gender differences;
iv. Co-exposure to high intensity static magnetic field, time-varying magnetic field gradients, and radio frequencies during examinations.
v. Toxicity rising from deposits of other lanthanides present as impurities in the GBCAs.
vi. The presence of an exogenous compound in the patient's body (e.g.; prostheses or implants, particularly breast implants).

Known and suggested parameters are listed in table 1.

4.1. Off-label use

A faulting mix might occur in the setting of the off-label use of GBCAs. Off-label use can be related to unapproved indication, dose, dosing schedule or rate and route of administration of GBCAs [148]. Approval of contrast agents officially follows the same avenue of drugs with therapeutic effects [148]. GBCAs are approved for specific body indications and applications [7], the label is guidance for use with information on the dose and indications [148]. Anyway, off-label use is routinely practised at imaging centers [1,7,149]. The adverse potential of this practice has been somehow underestimated. As early, as 2008, Reimer and Vosshenrich observed how many agents were not approved for the current spectrum of their clinical applications [148]. Also, the financial burden associated with the approval has been pointed out [148]. Again, Tamburrini and colleagues in 2011 highlighted poor investigation of the off-label use of contrast media, in particular, deviations from recommended dose that commonly, but not exclusively, applied to magnetic resonance angiography as well as cardiac and paediatric applications [1]. Repeated high-dose administration might trigger dose-related adverse reactions and metabolic abnormalities: Wolansky et al. reported that serial administration of triple-doses of GBCAs was associated with hypophosphatemia in a cohort of multiple sclerosis patients [150].

4.2. Rate of administration

The rate of administration might be one of the neglected parameters able to explain the dissociation of complexes with recognized higher stability (i.e.; macrocyclic agents), but also the condition able to exacerbate the liability of the linear complexes. The injection rate should be reported in each study, yet literature contributions often lack specifying the injection rate. Recommended injection rate is 2-3 ml/s (0.5 mmol/ml) [11]. However, there are specific studies that are known to require higher rates and high doses and/or higher concentrations of the agent to enable the acquisition of an adequate signal. It is the case of cerebral perfusion studies wherein a robust and compact bolus arrival in the cerebral tissue is required [149,151]. Automated injection is also required [151]. In these requirements, the injection rate reaches 5 ml/s, that is the double of the mean standard rate of delivery, and often it is combined with agents formulated at high concentration (i.e., Gadovist 1.0 mmol/ml gadobutrol). Lacking to report the concentration in literature contributions can create biases in the evaluation and comparison of different studies when there exist agents available

at different formulations. It is the case of gadobutrol formulated as Gadovist 1.0 mmol/ml or 0.5 mmol/ml, reported in the past [11]. For instance, Lee and colleagues [152] reported perfusion performed with Dotarem 0.5 M (gadoterate meglumine). The authors report a standard single dose of 13 ml and double dose for perfusion studies: It follows that the dose is not proportional to body weight as it is in most studies and protocols. Lin and Brown [9] reported injection rate up to 5 ml/s for cerebral perfusion studies at their own institution in 2008 and high dose (up to 0.3–0.4 mmol/kg) at concentration 0.5 M.

The same injection rate referred to a medium formulated at a double concentration means a double amount of gadolinium injected in the body per second. Even if the total dose of the gadolinium administered is the same, the two conditions are different. (To making this note clearer, this is a numerical example: a double minimum standard dose (i.e.: 0.2 mmol Gd/kg body weight) of a low-concentration agent (such as macrocyclic Dotarem 0.5 mmol/ml) means a total administered volume of 0.4 ml/kg body weight; the same dose of an agent formulated at higher (double) concentration, such as gadobutrol 1.0 mmol Gd/ml, means a half total volume administered, that is 0.2 ml/kg body weight. In the former case the standard flow rate of 2–3 ml/s means 1–1.5 mmol Gd/s, while 2–3 mmol Gd/s in the latter. But, in the case of the administration at higher rate, 5 ml/s, 2.5 mmol Gd/s are administered in case of low-formulation at 0.5 mmol Gd/ml and 5 mmol Gd/s in the case of high-concentration (i.e.; 1 mmol/ml).)

4.3. Study design, risk factors and the evaluation of a possible individual susceptibility

Individual susceptibility to deposition might markedly vary among subjects. A recent study on gadolinium deposition in a large animal model has shown significative inter-subject variability: a double concentration of gadolinium has been retained in the cerebellum of one sheep with respect to another (58, 76, 116 ng x g^{-1}) even after a single injection of 0.1 mmol/kg of a linear complex, a dose comparable to that for a human patient [76]. These differences might be poorly understood just assessing mean values. The publication of raw data in parallel with mean values and processed data might be useful to unravel still unknown parameters of relevance.

The number of administrations, the time distances among them, and the time distance from the last administration are crucial parameters in the evaluation of gadolinium deposition and must be taken into account in the study design and data analysis. Since gadolinium deposition appears to be a complex process of still not known dynamics (i.e.; evolving over time in an unknown balance among retention and possible delayed excretion), it cannot be fruitfully understood in humans in the singularity of a time-point measurement. The evolution over a period of time should be considered, not just a comparison of the imaging data at the first and last time point.

4.4. Electro-magnetic field exposure, time-varying magnetic field gradient in conjunction with high intensity static magnetic field

The context for challenging adverse reactions possibly associated with GBCAs (and their long-term effects in humans) should not be confined to GBCA administration alone (as often addressed in animal studies and phase I studies). The whole context comprises GBCA administration in conjunction with exposure to electromagnetic fields in the clinic (i.e.; the application of radio-frequencies sequences and time-varying magnetic field gradients in the presence of high

intensity static magnetic field soon after injection of GBCAs [153]). The whole topic is “toxicity associated with gadolinium-based contrast enhanced examinations" not only “GBCA administration". Cho et al. showed that exposure to electromagnetic fields adds gadolinium-associated cytotoxicity and genotoxicity to toxicity of gadolinium alone [154]. In turn, the specific condition of GBCA administration in subjects who already have gadolinium in their tissues should be taken into account. Also, the role and impact of increasing electromagnetic fields exposure in normal life should be included in the evaluation of delayed adverse effects associated with gadolinium retention in the body.

4.5. Metal toxicity as a whole and threshold for symptom onset

Even though it is easier to measure metal concentrations in animals, elucidating the clinical manifestations in animal models can be more challenging [155]. Furthermore, the issue of metal toxicity in animals may be not reflective with regard to the actual exposure in humans that are simultaneously exposed to more than one metal coming from the environment, its contamination by anthropogenic activities, drug exposure [155], and the presence of prostheses or metal dental restorative materials. The effects of the combination of different metals potentially toxic may be of clinical relevance, despite the concentration of each one being estimated irrelevant.

Combined chronic or long-term effects are more difficult to disentangle, particularly when no single high-level exposure or acute reaction occur, but cumulative storage. As mentioned above, on-going inflammation facilitates gadolinium retention into brain tissue [147], as a consequence, the data from healthy animal models possibly underestimate the deposition in human patients. Manifestation of toxicity depends from the amount, speciation of deposits, and compartment where they are stored. Retention of a small percentage following the administration of a single standard dose may be too low to induce any observable clinical manifestation. This might partially explain the lack of reported symptoms in studies showing deposits in healthy volunteers, such as those by Lord et al. [97]. The issue of cumulative administrations has been already pointed out, but not specific guideline or time schedule have been published, such as an inferior limit for subsequent administration: FDA recommended minimizing “repeated GBCA imaging studies when possible" and “particularly closely spaced MRI studies". However, the recommendation was also to “not avoid or defer necessary GBCA MRI scans" [156]. Nevertheless, it is at the same time important that the patient is really aware of the possible risks and benefits of the proposed treatment through the information provided by the physician when obtaining written informed consent [1].

Veiga et al. [157] measured rare earth (RE) impurities in commercial GBCAs: they found RE as impurities in all the samples analysed. The levels varied among both the elements and the agents and the differences can be considerable. The concentrations are higher for elements close to Gd, i.e. Eu and Tb, but also for La in Gavovist and Viewgam. Lanthanum impurities might be of relevance particularly for deposition in the bone [120]. Toxicity rising from deposits of other lanthanides present as impurities in the GBCAs deserves to be taken into consideration.

4.6. Gender differences

The issue of gender deserves specific attention, involving hormonal issues and also the dose. Females seem to be more exposed to adverse effects associated with gadolinium deposition [112]: it

should be understood if this is correlated to a higher retention or not. The issue of administered doses —now based on body-weight independently from the gender that is only indirectly considered thanks to the gender correction in the evaluation of estimated GFR from blood creatinine (i.e. factor 0.8 [158])—merits to be better evaluated to understand if a risk of over-dosage exists in women. The ratio among muscle mass and fat mass—possibly accessed in the practice by body-mass-index (BMI)—might be also better considered. Khairinisa [143] showed higher total gadolinium concentration in female mice, although behavioural alterations were not always more severe in females. Increasing evidence shows that health effects of some toxic metals differently manifest in male and female [143]. It is increasingly important to take into account gender differences when evaluating toxic insults.

4.7. Clinical and environmental exposure

GBCAs are exclusively approved for use in conjunction with a diagnostic procedure [7]: primarily, nuclear magnetic resonance examinations - taking advantage from the relaxation effect of Gd^{3+} [8]. But, it is worth to recall that prior to the recognition of NSF, GBCAs have been also used in conjunction with computed tomography (CT) as an alternative agent to iodinated contrast media in patients with impaired renal function or in patients with iodine allergy-taking advantage from the X-ray absorption properties of Gd^{3+} [9,159]. This practice enlarges the cohort of patients that could have been administered with GBCAs in their clinical history and, in turn, to be considered when investigating long-term effects associated with GBCA administration.

Moreover, the growing environmental contamination with anthropogenic gadolinium from GBCAs [160–162] opens healthy issues in healthy subjects of worldwide population and live-beings.

The impact of these compounds has been already showed worrying effects on marine wildlife [163–166]. Contamination of water and soil and penetration into human and animal food chain are a concerning reality [160,161,167].

5. Summary and conclusion

Known and emerging adverse reactions associated with administration of GBCAs have been reported. GBCAs are a staple of medical radiology with a good safety profile with respect to other contrast agents. Nevertheless, the evidence of gadolinium deposition has opened a vivid debate on possible still unrecognised adverse effects of these drugs, particularly those long-term. A great number of studies has investigated deposition, but, till now, very few have assessed the delayed and long-term effects. In addition, the physico-chemical mechanisms involved in the process of deposition have not been fully elucidated. Yet, the most urgent gap to fill concerns the existence of clinical/health implications. A rich research road-map is ongoing. Still the consensus lacks as much as longitudinal studies, but initial evidence of health effects has been published. Here, we have presented a critical analysis pointing out biases to overcome. Also, we have suggested parameters/conditions still poorly considered that deserve further investigations. They might be able to explain discrepancies and conflicting results among different studies and possibly help in a profitable planning of the future ones. Disentangling and recognizing the pathological potential of gadolinium-associated toxicity is of primary relevance in patients, but it might be of wider interest because of the growing environmental contamination from GBCAs.

Conflict of interest

The authors declare no conflict of interest.

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