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CONTRAST MEDIA

Standardized assessment of the signal intensity increase on unenhanced T1-weighted images in the brain: the European Gadolinium Retention Evaluation Consortium (GREC) Task Force position statement

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Abstract

After the initial report in 2014 on T1-weighted (T1w) hyperintensity of deep brain nuclei following serial injections of linear gadolinium-based contrast agents (GBCAs), a multitude of studies on the potential of the marketed GBCAs to cause T1w hyperintensity in the brain have been published. The vast majority of these studies found a signal intensity (SI) increase for linear GBCAs in the brain—first and foremost in the dentate nucleus—while no SI increase was found for macrocyclic GBCAs. However, the scientific debate about this finding is kept alive by the fact that SI differences do not unequivocally represent the amount of gadolinium retained. Since the study design of the SI measurement in various brain structures is relatively simple, MRI studies investigating gadolinium-dependent T1w hyperintensity are currently conducted at multiple institutions worldwide. However, methodological mistakes may result in flawed conclusions. In this position statement, we assess the methodological basis of the published retrospective studies and define quality standards for future studies to give guidance to the scientific community and to help identify studies with potentially flawed methodology and misleading results.

Key Points

- *A multitude of studies has been published on the potential of the marketed GBCAs to cause T1w hyperintensity in the brain.*
- *The gadolinium-dependent T1w hyperintensity in the brain depends on patient's history, types of GBCAs used (*i.e., *linear* vs. *macrocyclic GBCAs) and MR imaging setup and protocols.*
- *Quality standards for the design of future studies are needed to standardize methodology and avoid potentially misleading results from retrospective studies.*

Keywords Contrast media · Gadolinium · Magnetic resonance imaging · Dentate nucleus

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Abbreviations

ACR	American College of Radiology
DN	Dentate nucleus
EMA	European Medicine Agency
ESUR	European Society of Urogenital Radiology
FDA	Food and Drug Administration
GBCA	Gadolinium-based contrast agent
GP	Globus pallidus
GREC	Gadolinium Retention Evaluation Consortium
NSF	Nephrogenic systemic fibrosis
SI	Signal intensity
T1w	T1-weighted

Background and framework

In 2014, Kanda et al [1] reported a correlation between the number of gadolinium-based contrast agent (GBCA) injections and the increase of the dentate nucleus (DN)-to-pons and globus pallidus (GP)-to-thalamus signal intensity (SI) ratios on unenhanced T1-weighted (T1w) magnetic resonance imaging (MRI). Subsequent studies on human tissue found a positive correlation between the MRI signal changes and gadolinium concentration. Retrospective analysis at a multitude of sites revealed that gadolinium retention in brain structures in patients with normal renal function and intact blood-brain barrier has been occurring for the last 25 years without being noticed.

The majority of MRI studies [1–63] were focused on SI changes in the DN. Due to the relatively simple setup of such studies, retrospective imaging studies have been conducted worldwide at multiple sites. These studies provided evidence that (i) linear GBCAs are correlated with a SI increase in the DN if a certain number of injections (probably 5–6 injections) is exceeded; (ii) non-ionic linear GBCA gadodiamide causes a stronger SI increase than ionic linear GBCAs gadopentetate and gadobenate, and (iii) macrocyclic GBCAs are not or only weakly associated with SI increase compared to linear GBCAs (Fig. 1).

Notably, the majority of dentate studies found the SI increase to be dose-dependent for linear agents with a greater deposition associated especially with the weaker chelates such as gadodiamide (Omniscan®, GE Healthcare) and gadopentetate dimeglumine (Magnevist®, Bayer Healthcare) and in the presence of renal impairment. Indeed, the more stable macrocyclic GBCAs, gadoteridol (ProHance®, Bracco Imaging), gadoterate meglumine (Dotarem®, Guerbet), and gadobutrol (Gadovist®, Bayer Healthcare), have not been associated with substantial MRI changes in the majority of published studies, suggesting that the molecular structure of the GBCA ligand, whether linear or macrocyclic, is a crucial factor for the increase in signal intensity. When interpreting MRI studies, the inherent limitations of this technique to assess gadolinium in human tissues should be acknowledged.

A comparison between different imaging studies is often hampered by different methodological approaches, and stakeholders' interests can influence the debate by specifically presenting the publications that provide the desired results. The lack of systematic collection of data, the limited number of patients in single-center studies, and the varying technical setup and MRI sequence parameters among different institutions make data meta-analysis challenging if not impossible.

The current consensus paper aims to provide a guideline for retrospective MRI studies to guarantee a minimum level of standardization to achieve higher accuracy and maximize reproducibility. We highly urge editors and authors to comply with these standards to avoid the dilution of the scientific debate by flawed publications.

Fig. 1 Color map of currently published retrospective clinical studies on gadolinium-related brain T1w hyperintensity. Red: dentate nucleus (DN) signal increase with visible hyperintensity (unconfounded GBCAs); Light red: DN signal increase or visible hyperintensity (confounded GBCAs); Orange: DN T1w signal intensity increase without visible hyperintensity (unconfounded GBCAs); Light green: No DN signal increase or visible hyperintensity (confounded GBCAs); Green: No DN signal increase with no visible hyperintensity (unconfounded GBCAs)

Scientific context

In the period between 2014 and 2018, 63 original retrospective studies [1–63] were published all over the world, regarding the relationship between T1 high SI on brain MRI studies and exposure to intravenously injected GBCAs.

Available literature found that the signal changes in certain central nervous system structures identified with MRI, first and foremost the DN, correlated positively with the exposure to linear GBCAs. It is under debate if macrocyclic GBCAs can cause any SI increase (Fig. 1).

Even though retrospective studies can be highly qualified, the level of evidence provided from any study reporting on T1w hyperintensity depends primarily on uniform imaging protocol, scanners, time periods in which the follow-up examinations are performed and the number of included patients. Studies assessing identical imaging parameters and MR scanners at regular follow-up intervals provide a much higher level of evidence than studies that do not control for these parameters. Even though evidence from retrospective studies is generally classified as levels 3b (individual case-control studies), 4 (case series), and 5 (expert opinion) according to the Centre for Evidence-Based Medicine, Oxford, they can therefore provide a higher level of evidence than prospective studies that do not control for these parameters. Given the current body of evidence, it is likely that prospective, blind, controlled randomized studies would not significantly change the consistent results of the numerous available retrospective studies on the potential of GBCAs to cause T1w hyperintensity. Nevertheless, type I (false positives findings) and type II errors (false negative findings) may flaw study results and data interpretation (Table 1). Editors need to evaluate methodology used in retrospective studies across the world due to the heavily increasing number of published studies on this topic.

Although no definitive symptoms or diseases linked to the T1w hyperintensity in the gadolinium-exposed population have been reported, data on long-term effects is still limited, and further research is needed [64].

To date, nephrogenic systemic fibrosis (NSF) still represents the only well-established clinical entity related to toxic effects of gadolinium and occurs in patients with severe impairment of renal function after exposure to certain GBCAs.

Several papers have been published recently and presumably many will follow as radiological institutions are interested to

Chemical Structure	Linear Non-Ionic		Linear Ionic			Macrocyclic Non-Ionic		Macrocyclic Ionic
Molecule	gadodiamide	gadoversetamid	gadopentetate dimeglumine	gadobenate dimeglumine	gadoxetate disodium	gadoteridol	gadobutrol	gadoterate meglumine
Marketed as	*Omniscan*	*Optimark*	*Magnevist*	*MultiHance*	*Primovist*	*ProHance*	*Gadovist*	*Dotarem*
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explore their available database and verify the prevalence of MRI findings or clinical correlates in the whole or in specific populations after repeated exposure to GBCAs.

While radiologists consider providing diagnostic imaging with contrast-enhanced MRI a professional and ethical obligation, there is an equal obligation to protect patients from the potential risk of side effects related to this diagnostic procedure.

The current guidelines adopted by regulatory agencies (EMA, European Medicine Agency; FDA, Food and Drug Administration) and scientific societies (ESUR, European Society of Urogenital Radiology; ACR, American College of Radiology etc.) are relevant and of great importance in the clinical management of patients with renal insufficiency. However, methodological aspects are crucial to harmonize data and support decision-making both at preclinical [65] and clinical level [66]. In fact, recommendations on how to design and report data from clinical studies on gadolinium-induced brain T1 hyperintensity are currently missing.

Evidence from preclinical research

The appearance of T1w hyperintensity in the dentate nucleus of the cerebellum and in other brain areas is under debate as it has been used as an MRI correlate of gadolinium deposition in the brain and to compare different GBCAs. The data available from the scientific literature may appear not consistent among MRI studies; the retrospective nature of the studies and variables depending on patient's history, types of GBCAs used (confounded vs. unconfounded), and MRI protocols affect the results.

The currently prevailing theory of the development of gadolinium-dependent T1w hyperintensity is based on animal studies that found gadolinium in three different forms: the intact chelate, precipitated gadolinium, and gadolinium bound to macromolecules [65, 67, 68]. While the intact chelate was found for both—linear and macrocyclic chelates—precipitated gadolinium or gadolinium bound to macromolecules was found exclusively for linear GBCAs [69]. A recent study reported a washout of the intact chelate for the macrocyclic GBCA gadoterate (with no gadolinium above the level of detection after 6 months) while pharmacokinetic analysis suggested that gadolinium bound to macromolecules might stay permanently in the brain [68, 70]. Since, at least at the magnetic fields used in clinical practice, precipitated gadolinium should not cause T1-shortening and gadolinium bound to macromolecules causes a strong T1-effect, it is very likely that gadolinium released from the less stable linear agents that subsequently binds to macromolecules is the cause of the observed T1w hyperintensity seen with linear GBCAs. The accumulation of gadolinium in the DN and other structures might further be explained by the increased metal content in these areas, facilitating transmetallation.

In contrast, the intact chelate might only cause a temporary signal intensity increase during the washout phase of the chelate. The pathway of the intact complex through the brain is not completely understood, but there is accumulating evidence that gadolinium gets into the CSF through the choroid plexus and reaches the brain through the glymphatic system. It is important to point out that animal studies provided evidence that a comparable amount of all GBCAs reaches the brain and might cause T1w hyperintensities on its way through the glymphatic system [68, 71]. However, T1w hyperintensities in metal-rich areas should exclusively appear if the gadolinium is released from its complex. Hence, it is not expected that the intact chelate will accumulate in the DN or other metal-rich structures. These considerations underline the importance of the appearance of a visible dentate hyperintensity on unenhanced T1w images and do not give a theoretical basis for a long-lasting signal intensity increase (that is not caused by the temporary presence of the intact chelate) if no gadolinium accumulation can be found.

It should be emphasized that the T1w signal intensity increase in the brain might represent an indicator of the gadolinium release in the whole body. Especially the bone and skin [72–74] have been identified as areas of gadolinium deposition.

In summary, multiple biochemical and physiological mechanisms can modulate relaxivities in the living tissues such as macromolecular binding, water access, aggregation/precipitation, and cellular internalization. These effects are complex and do not affect T1, T2, and T2* relaxivity the same way. Thus, a fraction

Table 1 Type I and Type II Errors in Data Interpretation of Signal Intensity of the Dentate Nucleus and other brain sites after repetitive administrations of GBCAs

Type I errors	Type II errors
Disease mechanisms	MRI Technical aspects (e.g., GRE vs. SE sequences)
Age effects	Age effects
Confounded GBCAs (e.g., exposure to linear GBCAs in studies focused on macrocyclic GBCAs)	Confounded GBCAs (e.g., exposure to macrocyclic GBCAs in studies focused on linear GBCAs)
Presence of other minerals (e.g., Ca^{2+}, Fe^{3+}, Cu^{3+}, Mn^{2+})	Fe^{3+} effects on SI on T1 weighted images
Macromolecular complexes with high T1 relaxivity	Lower T1 relaxivity at higher magnetic fields (e.g., 3.0 T vs. 1.5 T)
	Absence of signal from precipitated Gd^{3+} salts in tissue

of the deposited gadolinium will remain invisible on T1w images. Multiparametric MRI analyses (e.g., with combination of T1, T2, and T2* or quantitative magnetic susceptibility mapping) may be used in future studies to disentangle these combined effects.

Recommendations

Results of the analysis of current literature indicate that knowledge gaps exist and recommendations are needed to systematically collect data in the experimental design of scientific studies [64, 75]. In November 2016 and 2017, the 1st and 2nd European Gadolinium Retention Evaluation Consortium (GREC) meetings were held in Naples (Italy) and Lisbon (Portugal), respectively, under the patronage of the European Society of Neuroradiology, with the intent to join the efforts of scientists from academy and industry and improve the understanding of the mechanisms of gadolinium retention/deposition/accumulation in the brain and non-brain tissues and, if any, its relationship with clinical symptoms in patients exposed to GBCAs [64]. In 2016, the GREC commissioned a Task Force to review the evidence regarding the gadolinium-dependent T1w hyperintensity in the brain and the methodology used to assess gadolinium retention in the brain in clinical studies.

In developing this position statement, the GREC and its Task Force assessed the methods applied to the measurement of T1w high SI in the brain in retrospective studies and found a lack of consistency in methodology across different institutions.

National and international scientific societies may use this recommendation to solicit and design harmonized multicenter studies that are aimed to explore indirect MRI measures of gadolinium retention/deposition in the brain. Regulatory agencies and scientific journal editors could use these recommendations to verify the methodology used in clinical studies. Finally, scientists will find a reference and a tool for the design and development of clinical studies.

Recommendations for the study design and interpretation of MRI results in clinical studies

Since restriction policies on the use of contrast agents must be evidence-based and excessive restrictions can have negative implications for healthcare, the GREC Task Force proposes the following specific suggestions (summarized in Table 2) to conduct clinical studies that assess brain MRI changes following repetitive intravenous administrations of GBCAs and to increase data homogeneity among different institutions.

1. GBCA administration has to be registered and traced over time to allow comparison of gadolinium retention-dependent signal. Institutions must have unequivocal proof of the type and dose of GBCA administered in each examination. If an institution has shifted from the single use of one GBCA compound to the single use of another one, shift dates should be clearly defined and documented. Authors have to exclude exposure to other GBCAs in the assessed period unequivocally by chart review. If they cannot exclude exposure to other GBCAs in the assessed period of time, they clearly have to state this.
2. Only SI differences between two specific MRI studies or intra-individual serial evaluation of multiple MRI studies should be assessed. Since absolute SIs are not reliable to assess gadolinium retention based on the influence of many parameters such as coil sensitivity, coil filling factor, head positioning within the coil, coil tuning/matching drift, MRI parameter drift, hardware and software gain, only relative SIs should be assessed. If available, a control group which got either a different GBCA or no GBCAs at all might be assessed.
3. Since the relevant parameter is the SI change, patients with pre-existing hyperintensity due to the prior injection of linear GBCAs can be included even if they display T1w high signal intensity at baseline. However, the authors need to provide documentation or state that they cannot exclude that the patients received other GBCAs prior to the inclusion in the study. A subgroup analysis may need to be conducted to exclude influence of previous GBCA injections or other confounding disease processes.
4. The average number of injections and the time between injections need to be documented clearly.
5. The DN has been shown to be the most sensitive structure for gadolinium deposition. Thus, studies that assess gadolinium retention in the brain should focus on this structure. If no SI increase is found in the DN, it is unnecessary to assess any further structure in the brain. If an SI increase in the DN is found, further structures (such as the GP) might be assessed.
6. The DN-to-pons ratio should be assessed in all studies since this is the most often used ratio in previous studies. Additionally, the DN-to-middle cerebellar peduncle (MCP) ratio can be used. The reliability of these measures is mainly based on the observation of less gadolinium deposition in the pons and middle cerebellar peduncles compared to DN in autopsy studies.
7. Regions of interest (ROI)-based approaches have been the most used and are expected to be used in future retrospective analyses. Generally, an extremely low inter-rater variability of this approach has been reported in previous studies if conducted appropriately. Since the DN is better depicted on T2w or diffusion-weighted images, these should be used as reference for placing ROIs. Since ROI drawing remains operator-dependent and used to obtain relative SI ratios, intra-rater and inter-rater agreement might be conducted as internal quality check.

Table 2 Recommendations to design retrospective studies on changes of signal intensity on unenhanced T1-weighted images after repetitive intravenous administrations of GBCAs

Institution	- Provide unequivocal proof of the type and dose of GBCA used in each examination.
Patients	- Group patients by age; separate pediatric (< 18 years) from adults.
	- Group patients by disease and report on interval treatment in the period of study
	- If a T1w SI increase is observed, exclude conditions or disorders commonly associated with brain deep gray matter T1 hyperintensity (parenteral feeding, exposure to manganese, porto-systemic shunts, neurofibromatosis etc.)
GBCAs	- Exclude the exposure to other GBCAs than that object of the study in the assessed period of time.
	- State clearly the average number of injections and the time between injections
MR imaging parameters	- Indicate MR technical parameters in the methods section as prescribed in recommendation 9.
	- Do not calculate SI change between different MR pulse sequences.
	- Accept a variation for TR and TE values up to 3.5; changes above 15% should be excluded. Subgroup analyses should be conducted to exclude a potential bias.
Quantitative ratios measurements	- Report on DN-to-pons ratios.
	- Additionally you might use DN-to-middle cerebellar peduncle ratio.
	- Intra-rater and inter-rater agreement for ROI measurements are generally very high. They might be conducted for internal quality check.
SI change	- Calculate SI change between scans with identical field strength.
	- Assess exclusively SI differences/changes measured with comparable technical parameters (see below)
	- Compare signal intensities of single MRI studies only between age-matched groups without GBCAs exposure and with identical imaging parameters at the same MRI scanner.

GBCA gadolinium-based contrast agent, *SI* signal intensity

8. Performance of automatic segmentation techniques in comparison to ROI techniques might be considered. Due to the low reported inter-rater variability of the ROI-based approach, it is questionable if the automatic approaches might provide additional value. However, this approach could be useful for the assessment of large datasets and of studies that provided unexpected results (e.g., high SI increase without any visible hyperintensity or no SI changes with visible hyperintensity).
9. Quantitative analyses such as T1 and T2 relaxivity mapping may be used additionally. It is currently unclear if they can provide additional value.
10. Since several technical parameters can affect the MR signal, investigators should indicate in the methods section a detailed table with the MR parameters: B0 static magnetic field, MR magnet vendor, coil type and number of coil channels, gradient strength, type of pulse sequence (e.g., Spin Echo (SE), Fast/Turbo Spin Echo (FSE or TSE), Gradient Echo (GRE), Inversion Recovery (IR), Magnetization Prepared Gradient Echo (MP-RAGE), type of prepulse, type of phase encoding (2D or 3D), Fourier transformation algorithm, repetition time (TR), echo time (TE), inversion time if applicable, flip angle, slice thickness, voxel volume, field of view, matrix, number of averages, and receiver bandwidth.
11. The SI ratio difference can only be calculated between MRI examinations that use identical imaging parameters and field strengths. Variation for TR and TE values between exams should be kept as small as possible. The maximum threshold of 3.5% of variation has been proposed as acceptable [24]. For high levels of parameter variations, subgroup analyses need to be performed. Variations of TR and TE above 15% should be excluded [24]. The SI ratio difference cannot be calculated between different pulse sequences or magnetic field strengths.
12. All studies should check if there is a visible SI increase in the DN in all patients that cannot be explained by confounders. Studies that report a high SI increase without corresponding visibility of this increase might be flawed (e.g., measurement of aging-related changes). The same holds true for studies that find clear visible SI increase in some patients but did not find a statistically significant SI increase.
13. Even though no clear correlation between SI increase and symptoms has been shown for most diseases, as a general recommendation, it is appropriate to evaluate and compare groups of patients with similar diagnoses. The available data do not allow understanding, at this point, of what is the contribution of the underlying pathologic process (brain tumors, chronic inflammatory diseases) on gadolinium retention and deposition. In addition, pediatric patients should always be treated as a distinct group for analysis.
14. Age of the patients included into retrospective studies should always be reported. This is crucial especially in pediatric patients that should be treated as a distinct group for analysis.

15. In studies that report a SI increase, it is mandatory to consider the confounders of conditions that increase the concentration of manganese in the deep gray matter (parenteral feeding, exposure to manganese, porto-systemic shunt) or certain disorders associated with an increase of the SI of the basal ganglia (neurofibromatosis type I, metabolic disorders, hypoxic-ischemic encephalopathy, etc.). The influence of radiation as a confounder is still a topic under investigation [52].

Conclusions

There is a broad consensus that radiologists should use GBCAs with the minimum effective dosage and only when strictly clinically indicated. At the same time, every effort should be made to protect patients from any side effect related to retention or exposure to GBCAs, and concern for public safety is paramount, particularly in children and patients who need several follow-up exams.

It must be underlined that there is currently no evidence of clinical consequences after exposure and retention of gadolinium in brain and non-brain tissues of patients with normal renal function, but any potential gadolinium-induced toxicity should also not be underestimated.

The current recommendations are a joint international effort (GREC) to increase the comparability of the huge number of retrospective studies that are currently published on SI increase on T1w MRI following serial injections of GBCAs. We encourage authors to follow these recommendations and editors and reviewers to evaluate the methodology of the papers submitted for publication to peer-reviewed journals as there is a need of data homogeneity and standardization on this topic.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Carlo C. Quattrocchi, Departmental Faculty of Medicine and Surgery, Head of the Unit of Diagnostic Imaging and Interventional Radiology, Università Campus Bio-Medico di Roma, Rome, Italy.

Conflict of interest The authors of this manuscript declare relationships with the following companies:

C.C. Quattrocchi has received speaker honoraria from Bayer Healthcare; has organized the 1st and 2nd European GREC meetings in 2016 and 2017 sponsored by Bayer, Bracco, GE, and Guerbet.

J. Ramalho has organized the 2nd European GREC meeting sponsored by Bayer, Bracco, GE and Guerbet.

A. J. van der Molen has received chairman honoraria from Guerbet; has organized the 1st and 2nd European GREC meetings in 2016 and 2017 sponsored by Bayer, Bracco, GE, and Guerbet.

À. Rovira serves on scientific advisory boards for Novartis, Sanofi-Genzyme, Icometrix, SyntheticMR, and OLEA Medical, and has received speaker honoraria from Bayer Healthcare, Sanofi-Genzyme, Bracco, Merck-Serono, Teva Pharmaceutical Industries Ltd., Novartis, Roche, and Biogen Idec.

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Informed consent Written informed consent was not required for this study because no original data were produced.

Ethical approval Institutional Review Board approval was not required because the paper is a recommendation statement and experiments were not performed.

Methodology International consensus statement on methodological recommendations on clinical studies

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