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REVIEW ARTICLE

T_1 hyperintensity on brain imaging subsequent to gadolinium-based contrast agent administration: what do we know about intracranial gadolinium deposition?

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ABSTRACT

There is growing evidence for the accumulation of gadolinium (Gd) in patients administered with intravenous Gd-based contrast agents, even in the absence of renal impairment. This review of the literature will discuss what has been found to date in cadaveric human studies, clinical studies of patients and from animal models. Evidence for the potential route of entry into the brain will be examined. The current state of knowledge of effects of Gd accumulation in the brain is discussed. We will then discuss what the possible implications may be for the choice of Gd-based contrast agents in clinical practice.

INTRODUCTION

Gadolinium (Gd)-based contrast agents (GBCAs) are a cornerstone of radiological MRI with >300 million patient administrations to date worldwide. Radiological practices changed following the emergence of an association between the administration of the less stable GBCAs in patients with severe renal impairment and the very rare condition nephrogenic system fibrosis (NSF). GBCAs have since been classified on the perceived risk of dissociation and consequent risk for Gd to be released.[1] However, widespread use of GBCAs continues, including those most frequently associated with NSF. Yet because of the response of the radiology community, avoiding the less stable linear chelate "high-risk" GBCAs in those patients known to be at greatest risk with severe renal impairments, no new cases related to exposure to the agents following the 2007 Food and Drug Administration (FDA) warning have been reported. There have been cases of NSF manifesting subsequent to the FDA warning that have been reported, but all associated with the administration of high-risk GBCAs in severe renal impairment prior to the FDA warning in 2007, essentially late presentations, although the reasons for these delays are obscure.[2,3] All diagnostic radiological practice involves a balancing of the estimated risk of an investigation *vs* the perceived benefits of the information to be gained from it. Recently, there have been a series of publications investigating signal hyperintensity on unenhanced T_1 weighted (T1w) MRI of the brain (involving the dentate nucleus and basal ganglia) in patients who have previously been administered multiple doses of GBCAs, which indicates that Gd may deposit long term in the brain. Have the scales just been tilted again?

GBCAs are used for contrast enhancement of MRI and for MR angiography because of the paramagnetic properties of the Gd ion with 7 unpaired electrons. Free Gd ions are known to be highly toxic hence their formulation as a chelated compound for intravenous administration. Gd^{3+} ions are the same diameter as Ca^{2+} and are capable of binding to many of the same sites as calcium.[4] GBCAs are made safe for clinical use by binding the ions to a ligand. The ligand binds tightly to the Gd ion permitting the excretion of the intact complex. GBCAs have the potential for dissociation of Gd from the chelate, releasing Gd ions into the patient although the formulation of the chelate is designed to absolutely minimize this. The chemical properties of the ligand molecule determine how likely this is, and the process is influenced by the environment of the molecule. For the GBCAs authorized in the EU, the most stable ones with the lowest potential for dechelation (conditional stability being the measure that matters in this respect) are the macrocyclic GBCAs. Data from both animals and humans have so far demonstrated that Gd can accumulate in a range of tissues and organs, including the

skin, bone, liver, kidney, muscle and spleen albeit in very low concentrations. However, the exact state of this Gd in terms of whether it has been dechelated and bound now to another compound or still as the intact original GBCA is not always clear, although it appears that dechelation does occur at least to some extent with the less stable high-risk linear chelates; this has not been shown with any of the macrocyclic GBCAs.[5,6] Table 1 lists the GBCAs available in the EU, their product name, the relevant generic name, risk category and structure.

Deposition of Gd in patients with severe renal impairment is associated with NSF, a condition first described in 2000, although the link to GBCA use for imaging was not made until 2006.[7–11] NSF is a serious, sometimes life-threatening, condition involving fibrosis, notably of the skin, and where this is across joints, mobility is reduced. In more severe cases, there is fibrosis of the internal organs such as the liver, lungs and heart with potential consequent morbidity and mortality. Prolonged elimination times in patients with severe renal impairment and release of Gd from ligand molecules are the main factors thought to be associated with the development of NSF, although other factors must influence this since only a small proportion of renal failure patients exposed to high-dose, high-risk GBCAs develop NSF.[11] This release of Gd is dependent on the chemical environment, so called conditional stability, which is pH dependent: acidic conditions promoting release.[12] Port et al[12] demonstrated greater conditional stability amongst macrocyclic GBCAs and with ionic rather than non-ionic GBCAs. There is no data on the effect of varying causes of metabolic acidosis on stability of GBCAs *in vivo*, although acidosis seen in renal failure is viewed as a contributor to the risk created by administering high-risk linear chelate GBCAs to patients with renal impairment. The clinical significance of other metabolic acidoses as potential promoters of dechelation of GBCAs is uncertain. The clinical significance of other situations associated with local drops in pH is also unclear. The pH of muscles may drop during exercise. The pH in pus can be very low, but furthermore, it is not known if free oxygen radicals created during the response to infection clinically affect the stability of GBCAs? Similarly, the pH in some tumours can be lower than normal tissue. Yet GBCAs, when not being used for MR angiography, are generally given to demonstrate or exclude enhancement from inflammation or tumours.

The mechanism by which Gd may accumulate in brain tissue is not known for certain although it has been demonstrated to cross the blood–cerebrospinal fluid (CSF) barrier, and it is not certain in what state this occurs and is accumulated. Maramattom et al[13] reported a case where a 57-year-old female with end-stage renal failure developed a reduced, fluctuating level of consciousness and mild left-sided weakness after repeated contrast-enhanced scans, and the exact dose was uncertain (but thought to be 60–80 ml) and, unfortunately, the specific Gd chelate used was not ascertained. Gd-related signal change was present in the CSF on MRI scan, and there was resolution after dialysis. Hui and Mullins[14] reported a similar case of a patient who underwent MRI and MR angiography with apparent CSF accumulation of contrast which was associated with encephalopathy but which resolved with dialysis, and although not specifically stated, the report suggests this patient also was in end-stage renal failure; again, the authors do not specify the particular contrast agent used or the dose employed. More recently, accumulation of perivascular spaces in the CSF has been reported in context of delayed post GBCA-enhanced MRI for endolymphatic hydrops in people with presumably normal renal function.[15] It has been postulated that once across the blood–CSF barrier, the GBCA would then enter the lymphatic system.[15] Whether this explains the preferential distribution with the dentate nucleus and globus pallidus is not clear.

The location relative to the blood–brain barrier (BBB) of the Gd may be important in determining the future risks to the patient. Is the deleterious effect, if any, of Gd to the brain tissue dependent on crossing the BBB in order to be toxic to the neurons or glia? Gd could potentially cross the BBB either because it is locally or diffusely permeable to the intact GBCA or of passage of the dechelated Gd, with or without the use of a transport

Table 1. Summary of gadolinium-based contrast agents available in the market

Product name	Generic name	EMEA NSF risk category	Structure
Magnevist (Bayer)	Gadopentetate dimeglumine	High	Linear ionic
Omniscan (GE HealthCare)	Gadodiamide	High	Linear non-ionic
Optimark (Mallinkrodt)	Gadoversetamide	High	Linear non-ionic
MultiHance[a] (Bracco)	Gadobenate dimeglumine	Medium	Linear ionic
Primovist[a] (Bayer)	Gadoxetic acid	Medium	Linear ionic
Ablavar[a]	Gadofosveset trisodium	Medium	Linear ionic
Dotarem (Guerbert)	Gadoteric acid	Low	Macrocyclic ionic
Gadovist (Bayer)	Gadobutrol	Low	Macrocyclic non-ionic
ProHance (Bracco)	Gadoteridol	Low	Macrocyclic non-ionic

EMEA, European Agency for the Evaluation of Medicinal Products; NSF, nephrogenic systemic fibrosis.
The data in the table are categorized by product name (by NSF risk category and alphabetical order of product name within category), active substance, NSF risk category and structure of chelating agent.
[a]These agents are categorized as medium risk even though they have not been linked unconfounded to any NSF cases, perhaps because of their dual hepatic and renal excretion and relatively higher stability constants than the other linear agents.

system. Common indications for the use of GBCAs are to demonstrate manifestations of the breakdown of the BBB, for example, in brain tumours and inflammation of the brain such as in infection or autoimmune disease. In these circumstances, the GBCA agent itself could accumulate in brain tissue without any chemical change. Equally, it could also represent a potential route for egress of the agent from brain tissue. In addition, workers such as Wardlaw et al,[16] Topakian et al[17] and Taheri et al[18] have suggested that GBCAs may cross the BBB in the context of endothelial dysfunction and small vessel disease. Wardlaw et al,[19] for example, assessed patients within a month after lacunar or cortical stroke. They found diffused increases in T_1 signal within the CSF, 30 min after the intravenous administration of gadodiamide. Given the population prevalence of small vessel disease and stroke, it suggests that the size of the population at risk of accumulating Gd by this potential mechanism is relatively large.

In their systematic review from 2014 of assessment of BBB disruption using contrast-enhanced MRI, the Wardlaw group identified 70 studies of which 45 had used gadopentetate dimeglumine, 15 had used gadodiamide, with 10 studies using a range of other agents including gadoterate meglumine, gadobutrol and gadoteriol.[20] There were no studies that presented comparison between these agents although the apparent demonstration of permeability of the BBB is clearly not limited to gadodiamide and gadopentetic acid. These studies also have implications for design of animal studies which need to reflect the clinical reality of the patients exposed to GBCAs, as has already been highlighted by Pietsch et al.[21,22] Alternatively, it is possible that if Gd accumulates in brain tissue, it does so after release from a reservoir such as bone given that there is evidence for Gd being present in small amounts in the skin and bone after exposure to GBCAs, including macrocyclic agents, even when renal function is normal.[23] This means that there is a potential for effects long after Gd exposure, for example, Thomson et al reported the development of NSF in a patient for more than 6 years following gadodiamide exposure, whereas Larson et al[24] reported NSF 10 years after Gd^3 exposure—the specific GBCA used was not stated in this report but highly likely to have been a high-risk GBCA given the period and geographical location in question. Thomson et al[3] have also reported delayed presentations of NSF from prior exposure to high-risk agents. The implications, if any, of long-term bone deposition for in utero exposure and breast feeding are unclear.

So why should Gd apparently particularly deposit in relation to the basal ganglia and dentate nuclei rather than at other sites in the brain? The dentate nucleus, particularly, is a depository for copper and zinc which are required for normal function, and these are known to chelate with diethylenetriaminepentaacetic acid.[25] Furthermore, it is known that transmetallation occurs with chronic exposure to both manganese and lanthanum (the latter, of course, a lanthanide of the same series as Gd in the periodic table) with subsequent neurotoxicity, therefore perhaps this is a similar process.[26–28]

Alternatively, as discussed above, the Gd^{3+} ion is the same diameter as a Ca^{2+} ion and is known to substitute for it in metabolic processes.[4,29,30] In this regard, it is interesting that the sites that Gd seems to accumulate in the brain are those that are most likely to calcify normally, the globus pallidus and the deep cerebellar nuclei (DCN) which includes the dentate nucleus. This naturally raises questions about what might influence such uptake into brain tissue. Are those conditions that promote calcification in the brain, such as hypoparathyroidism amongst many others, risk factors for increased Gd uptake? Birka et al[31] published evidence from a patient with proven NSF that Gd was codistributed with phosphorus in the skin and in vessel walls. Does the existing calcium (or associated phosphate) concentration in brain tissue affect deposition, and this might therefore suggest an increasing risk with ageing in those regions prone to calcification with normal ageing?

What is the actual evidence for Gd accumulation in the brain? There are essentially 4 areas of evidence which may be considered in a hierarchical way. Firstly, there are cadaveric studies where mass spectrometry has been used to measure Gd concentrations in human brain tissue from the cadavers of patients with documented histories of GBCA exposure in the past. Secondly, there have been human tissue studies which have demonstrated the presence of Gd with mass spectrometry in brain tissue obtained from patients with brain tumours at the time of neurosurgery and with recent exposure to GBCAs. Thirdly, there are non-clinical studies in animal models used to test hypotheses arising from the above studies and from the fourth group, clinical observational studies in specific patient populations.

CADAVERIC STUDIES

There are 2 cadaveric studies published which collectively report the results of analysis of pathological specimens from 18 post-mortem cases with good histories detailing GBCA exposure. McDonald et al[32] compared brain tissue at post-mortem examination from 13 patients exposed to gadodiamide (Omniscan) for brain MRI and with known contrast administration histories. All of the patients had had normal renal function at the time of GBCA exposures. The exposed group had received 4 or more administrations (up to 29) of gadodiamide between 2000 and 2014. All of the 13 patients exposed to gadodiamide for brain MRI had detectable Gd in brain tissue from the dentate nucleus, pons, globus pallidus and thalamus (0.3–58.8 μg per gram of tissue). Samples from 10 control patients who had not received GBCAs did not contain detectable levels of Gd. Changes in pre-contrast T_1 signal on MRI in the dentate nucleus strongly correlated with the amount of tissue Gd assayed with mass spectrometry ($r = 0.93$, $p = 0.0001$). McDonald et al[32] also investigated the localization of Gd within neuronal tissues and assessed for histological changes using transmission electron microscopy. They found that among Gd-exposed samples, Gd was prominently clustered in large foci within the endothelial wall with apparently only a small proportion having crossed the BBB into the neuronal interstitium itself. They also stated that "Despite direct evidence of Gd deposition within neuronal tissues, we were unable to detect gross histological changes between contrast and control groups in hematoxylin–eosin–stained tissues samples with visual light microscopy".

Kanda et al[33] have also reported that Gd was detected in post-mortem brain tissue samples by mass spectrometry in five patients who had all been exposed to multiple doses of linear chelate GBCAs. Samples from five control patients who did not receive GBCAs contained levels of Gd that were many fold lower/undetectable. The exposed group had received at least two doses of linear chelate GBCAs, and most of these were of gadopentetate dimeglumine. One patient had an additional exposure to gadodiamide and another patient had additional exposures to gadodiamide and gadoteridol. None of the subjects had abnormal renal function at the time of the GBCA administrations. Kanda et al[33] also demonstrated that after intravenous infusion, Gd accumulates in the brain, finding a mean concentration of 0.25 μg per gram of brain tissue ±0.44 (standard deviation). This is in good agreement with the evidence from McDonald et al.[32] The concentration of Gd was higher in the dentate nucleus and globus pallidus (mean, 0.44 $\mu g\,g^{-1}$ ±0.63) than in other brain regions (mean, 0.12 $\mu g\,g^{-1}$ ±0.16) ($p = 0.029$). However, the high-risk linear GBCAs gadopentetate dimeglumine and gadodiamide were the predominantly administered agents, and while the cyclic chelate gadoteridol was also used, in none of the patients was this agent used unconfounded with the linear agents, plus in these two patients, the measured Gd concentrations were lower than the mean.

Of particular note in both these cadaveric studies is that the levels of Gd detected are orders of magnitude lower than would be expected to give rise to visible signal on routine T1w brain MRI sequences. Therefore, even if low levels of Gd have been deposited in some form, why is hyperintensity visible on T1w brain imaging?

HUMAN TISSUE STUDIES

Xia et al[34] published a study of brain tumour biopsy samples evaluated using scanning electron microscopy/energy dispersive X-ray spectroscopy, which is a different technique to the cadaveric studies of McDonald et al[32] and Kanda et al.[33] The technique used by Xia et al[34] enables some spatial localization at the level of the scanned electron micrograph. The cadaveric studies used inductively coupled plasma mass spectrometry which has much higher sensitivity, several orders of magnitude greater, although it lacks the spatial localization as the tissue is converted to plasma for analysis. The brain tissue samples analysed by Xia et al[34] were from patients undergoing tumour resection who had received at least one MRI with gadodiamide. Some of the patients had further MRI scans with gadobenate dimeglumine, although again, none with this agent alone unconfounded with the high-risk gadodiamide. The brain tissue samples were taken at surgery performed soon after the last scan, median 1 day (range 0–9 days). Insoluble Gd was found deposited in association with phosphorus and calcium in seven specimens from five patients. These deposits were primarily in highly vascular areas, for example, frequently within the walls of blood vessels which given their location in a brain tumour are likely to have an abnormal BBB. The deposits were also found in association with calcification. Gd deposits were more common in biopsies from patients with more than one MRI scan. Of the biopsies included in the analysis, 31% (4/13) of those with more than one GBCA-enhanced MRI scan had deposits, whereas only 6.6% (1/15) of those with only one MRI scan had Gd deposits. This suggests longer term accumulation from prior scans as indicated by the cadaveric studies and not just a temporary phenomenon.

NON-CLINICAL ANIMAL MODEL STUDIES

Robert et al[35] reported T_1 signal hyperintensity in the DCN after administration of gadodiamide to healthy rats with normal renal function ($n = 7$). The rats were given 20 intravenous injections of 0.6 mmol of Gd per kilogram (4 injections per week during 5 weeks) of one of gadodiamide, gadoteric acid or saline (control group). However, it should be noted that this is very much higher and more frequent doses than would be given in normal clinical practice. T1w MRI of the brain was performed using a 2.35-T system before and once a week during the 5 weeks of injections and during 5 additional weeks (treatment-free period) to detect either persistence or any washout effects. Gd concentrations were measured with inductively coupled plasma mass spectrometry in plasma and brain (the same technique as in the cadaveric studies discussed earlier). A significant and persistent T_1 signal hyperintensity in DCN including the dentate nucleus was observed only in gadodiamide-treated rats. The T_1 signal increases detected persisted to the end of the 5-week treatment-free period. No quantifiable Gd was found in the plasma of rats at completion of the treatment-free period (*i.e.* 5 weeks after the last administration). The total Gd concentration was significantly higher (in the cerebral cortex, subcortical brain and cerebellum) in gadodiamide-treated rat than in gadoterate-treated rats. This study confirms that not all of the GBCAs behave the same with respect to brain accumulation and confirms the change in T_1 signal that has been reported in observational clinical studies. Jost et al[36] studied Wistar-Han rats dosed with either gadodiamide, gadopentetate dimeglumine, gadobenate dimeglumine, gadobutrol, gadoterate meglumin or saline as a control with the GBCAs administered in 25-fold doses compared with human clinical use. Rat brain imaging was performed at 1.5 T and showed signal hyperintensity after administration of the linear agents but not the macrocyclics or saline control. The gadodiamde-dosed animals also showed NSF-like skin changes, whereas none of the others did. Histology of the rat-brain deep nuclei showed no adverse histology in any of the subjects. Very low concentrations of Gd were found in the brain tissue 15-fold higher for the linear agents with levels in those administered macrocyclics extremely low. An extremely interesting finding from this work is that using chromatography of aqueous cerebellar homogenates, there was a peak indicating Gd bound to macromolecules in the 200–300 kD from the brains of rats administered with gadodiamide that was not seen with those administered with macrocyclic agents. This is strong evidence that for the gadodiamide-dosed rats, there has been dechelation with transmetallation of Gd to macromolecules and this could well explain the T1w signal hyperintensity at low Gd concentrations, as these macromolecules would be slowly rotating complexes with particular conspicuity at 1.5 T. What these macromolecules could be is of course uncertain at this time, but one suggestion has been that it could be neuromelanin.

If the GBCA manufacturers are in possession of other similar unpublished data covering the full range of marketed GBCAs in

clinical use, it should be incumbent upon them to make this publicly available in the view of the authors.

Kartamihardja et al[37] assessed Gd deposition in the brain of mice after multiple (20) injections of gadodiamide (Gd-DPT-BMA), gadoteric acid (Gd-DOTA), both at 5 mmol kg^{-1} or gadolinium (III) chloride at 0.02 mmol kg^{-1}. These are much higher doses than used clinically. In contrast to Robert et al,[35] when using T1w imaging performed at 1.5 T to visualize the deposition in the brain approximately 1 week after the 20th injection, no difference in the contrast-to-noise ratio could be determined. However, tissue Gd concentrations detected using inductively coupled plasma mass spectrometry showed gadodiamide was associated with the highest deposition in the brain and the skin compared with a macrocyclic GBCA comparator, gadoteric acid. No clinical effects or increases in skin thickness were identified associated with this study. This study also indicates differential rates of accumulation in the brain depending on the chemistry of the GBCA administered and that this may arise in the presence of normal renal function.

CLINICAL OBSERVATIONAL STUDIES

There are 11 separate clinical observational studies which report the findings from 681 patients in total including a study focusing on children.[38–48] All of the patients reported in these studies had normal renal function at the time of the administration of the GBCAs. The methodology employed to observe the effects of the presence of Gd in all these studies has been to measure changes of T_1 signal (not T_1 mapping) relative to a "control" area such pons, a peduncle or other white matter area. If the concentration of Gd in the brain reflects that seen in the cadveric studies, it is surprising that there was a measurable T_1 signal effect at all if it is a directly attributable phenomenon. However, more recent studies have now used T_1 and T_2 mapping to confirm the earlier studies reporting T_1 signal change.[47,48] The most likely emerging explanation for this comes from the pre-clinical work of Pietsch's group discussed above who have noted the following.[49] Firstly, T_1 signal hyperintensity is most prominent at 1.5 T imaging and less conspicuous if visible at all at higher field strengths. Secondly, in aqueous cerebellar homogenates from the brains of rats administered with gadodiamide, there is a chromatographic peak at 200–300 kD indicating Gd is bound to a macromolecule, a phenomenon not seen with the macrocyclic agents. Gd bound to such a macromolecule could well give rise to signal at 1.5 T even at low concentrations since it would exhibit slower tumbling, a mechanism akin to the increased relaxivity where agents such as gadofosveset bind to albumin in plasma. This effect rapidly reduces at field strengths higher than 1.5 T. This is strong secondary evidence that the Gd found in these deep nuclei are indeed due to Gd ions dechelated from the ligand caldiamide that is formulated in gadodiamide, an agent with much lower conditional stability compared with macrocyclic agents. Alternatively, the signal change may represent secondary changes such as alterations in iron or calcium concentration or even other elements such as manganese locally in those areas of Gd accumulation. Greater knowledge about the location and state of the Gd in tissue could be useful for identifying both the possible biological effects on the brain and the possible reversibility of the accumulation. Interestingly in mice, there appears to be very different rates of clearance of gadopentetate dimeglumine from different brain structures after a single bolus.[50] CSF and the subdural space are quickly cleared, but there is detectable gadopentetate dimeglumine for many hours in the cortex and subcortical grey matter.[50]

The indications varied for the administration of GBCAs between the different study populations across the studies. The main indication for an MRI scan with a GBCA was investigation for brain tumours, but some were for stroke and others multiple sclerosis. However, all of these groups of patients would be potentially expected to not have a fully functional BBB. Thus, it is possible that Gd accumulated in the brain at the time of the injection rather than redistribution from another site of sequestration. The majority of the studies reported findings from patients with a history of multiple exposures, most reporting five or more separate administrations. All studies report changes of T_1 signal in dentate nucleus and/or globus pallidus. In general, the studies show increase in T_1 signal proportional to increasing exposure. Increases in T_1 signal in the dentate nucleus and the globus pallidus have been frequently linked to gadodiamide and to gadopentetic acid exposure. One study shows decrease in T_1 signal after gadobenic acid.[40] Stojanov et al[44] demonstrated a change in T_1 signal in the dentate nucleus and the globus pallidus in a group of 58 patients with multiple sclerosis that had gadobutrol administered on average 4.74 times. The authors of this study hence suggest that the accumulation in the brain is not limited to linear chelated GBCAs. However, this study can be criticized on several counts, not least that there is no control for potential prior confounding agent administration, the correlation of 0.263 is very weak and there is no visible signal hyperintensity on any of the imaging supplied in the article.[51] Indeed, Radbruch et al[45] failed to demonstrate any T_1 signal change in the same brain regions of patients with repeated exposure to gadoteric acid. Thus, the evidence regarding the macrocyclic agents causing T_1 signal hyperintensity is currently far less strong than for the linear agents gadodiamide and gadopentetic acid.

The clinical evidence that Gd accumulation in whatever form is deleterious to the brain is surprisingly limited. Arlt et al[52] reported a case of toxicity following accidental intrathecal injection of the linear chelate gadopentetic acid. Short-term problems largely resolved, but the patient was left with "very mild" gait ataxia. Clearly, this case is potentially consistent with Gd accumulating in the dentate nucleus of the cerebellum, but there was no relevant imaging performed. The Maramattom et al[13] case report discussed previously indicated the Gd accumulation was associated with a fluctuating level of consciousness and mild left-sided weakness with resolution after dialysis. The patient in the report by Hui and Mullins[14] with apparent CSF accumulation of contrast also had encephalopathy which resolved with dialysis. There are also non-clinical studies that support linear chelate Gd-based contrast agent neurotoxicity when they are injected directly into the CNS.[53,54] However to date, in none of the studies where T_1 hyperintensity has been shown in the brain on imaging have any deleterious clinical effects been observed.

DISCUSSION

The studies reviewed present different lines of evidence that suggest that Gd may accumulate in brain tissue after intravenous administration of GBCAs in humans even in the absence of renal impairment although at very low concentrations (23 times lower than in the bone).[21] The amounts are significantly higher for the less stable linear chelate GBCAs that have been associated with the development of the rare disorder of NSF in patients with severe renal impairments. Only in patients exposed to multiple doses of these less-stable linear chelate GBCAs have visible signal changes been manifest in the brain (dentate nucleus and globus pallidus) on T1w MRI scans. In these patients, the Gd concentrations are lower than should give signal if still chelated as originally formulated, suggesting dechelation and transmetallation with the Gd ion passing to a macromolecule. Which clinical circumstances are clinically significant in promoting dissociation of Gd from its chelator and accumulation in the brain in the absence of renal failure, if any, represents a significant knowledge gap.

However, what is also absent at present is evidence for a clinical effect of the presence of Gd in the brain and in the dentate nucleus and globus pallidus in particular. Even in animal models, evidence for a toxic effect of Gd accumulation in rat brain tissue from multiple intravenous injections of both linear and macrocyclic contrast agents is currently lacking.[55] In no patient in whom T1w signal hyperintensity has been observed has there been associated clinical neurological sequelae. Where are the patients presenting with ataxia and movement disorders? Equally, how many patients worldwide were administered GBCAs before NSF was recognized? Are neurologists enquiring about exposure to GBCAs amongst their patients with idiopathic sporadic ataxia or with other movement disorders? Clearly, the fact that many of the patients administered multiple doses of GBCAs will have had such for the investigation of neurological conditions is a confounding factor for evaluation of any new subtle neurological problem.

Therefore, although there is growing evidence tilting the scales away from routine use of GBCAs further than previously if a precautionary approach is adopted, there is an important knowledge gap on the significance of Gd accumulation in the brain which needs to be addressed as a matter of urgency. There is clear evidence that the accumulation of Gd happens and that it varies depending on the agent in question. Furthermore, the accumulation is likely in different forms (dechelated and subsequently bound to macromolecules *vs* remaining tightly bound in original GBCA form), again dependent upon the class of agent in question. This will have important implications in terms of putative toxicity. This evidence for or against toxic effects needs to be strengthened, but the clinical community and health institutions have a duty of care. A circumspect approach is to limit or even avoid the use of GBCAs where possible. But given that the clinical significance of the indications for the radiological use of GBCA, the clinical need for a safe GBCA will remain. Indeed their clinical utilization is likely to remain widespread for the foreseeable future. In the UK, choice of GBCAs tends to be taken at an institutional level. This duty of care suggests that choice of GBCAs institutionally available cannot be entirely cost driven and that unless the distinct properties of a particular linear agent are specifically required (*e.g.* for liver or vascular imaging), then the preference should be for a "low-risk" macrocyclic agent.

CONFLICTS OF INTEREST

The views expressed in this article are those of the authors and not those of the BJR, MHRA or EMA. Both authors are expert advisors to the MHRA. This article represents the views and opinions of the authors themselves and not the MHRA. Neither author reports any financial conflict of interest.

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