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Adverse effects of gadolinium-based contrast agents in organ systems: a literature review

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ABSTRACT

Background and aim: Gadolinium based contrast agents are widely used materials in magnetic resonance imaging (MRI) diagnostic procedures. Gadolinium based contrast agents (GBCAs) are classified by structure to linear or macrocyclic. It is suspected that the difference of the structure may be responsible for the mechanism of side effects after MRI. The aim of this article is to assess the side effects of MRI contrast agents in various organ systems.
Materials and methods: The study was conducted by an electronic database subscription of Lithuanian University of Health Sciences: PubMed (Medline), EMBASE, ClinicalKey, ScienceDirect. We tried to review and summarize the published literature of GBCAs effect in various organ systems. Our research also carried out a forward citation and bibliographic search of identifying studies regarding nephrogenic systemic fibrosis (NSF), gadolinium deposition, gadolinium retention, gadolinium based contrast agents in the brain.
Results: There are evidence that linear GBCAs affect the body more than their macrocyclic structure. GBCAs cause uncommon conditions such as deposits in brain and NSF. NSF firstly affects skin and spreads to liver, bones, lungs and other organs.
Conclusions: Gadolinium based contrast agents should be under strict regulation just like other pharmaceuticals for their adverse effects and damage of organs structures. Therefore, these agents should be strictly monitored and reviewed case by case before administration to patients to avoid gadolinium accumulation in tissues and possible diseases.

Keywords: nephrogenic systemic fibrosis, gadolinium based contrast agents, magnetic resonance imaging.

BACKGROUND

Nowadays magnetic resonance imaging (MRI) is one of routine diagnostic methods. MRI has been proposed to have a role in diagnosis of various problems such as cancer, infections, soft tissue diseases, etc. This imaging technique can be performed with or without the contrast agents. Gadolinium based contrast agents (GBCAs) are used during the MRI scan as intravenous materials to improve imaging quality of organs and demonstrate their perfusion [73]. GBCAs can be non-specific extracellular gadolinium chelates or high relaxitivity agents/organ specific agents/protein bound agent [3,4,69]. The non-specific agents are secreted in kidney and they do not require protein binding. However, high relaxivity agents need protein binding and are excreted in kidney and bile.

Moreover, based on structure GBCAs can be classified as ionic or non-ionic, linear or macrocyclic. The chemical structure affects stability of the agent [5]. The difference of the structure is related to the stability of component. In recent years the rapidly growing body of data demonstrates that non-stable GBCAs may be one of the most important factors affecting pathophysiology of toxicity [7,8,9]. The dissociation of gadolinium determines the toxicity of material. The understanding of the mechanisms of gadolinium toxicity can help to determine the clinical significance of gadolinium retention in tissues [9]. Hence, the risks of GBCAs usage for MRI can be assessed better [9]. There are nine GBCAs currently approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) [70]. Out of those nine GBCAs the linear ones are gadofosveset (Ablavar, US only), gadoxetate (Eovist), gadopentetate (Magnevist), gadobenate (MultiHance), gadodiamide (Omniscan), gadoversetamide (OptiMARK). Three of them have macrocyclic structure: gadobutrol (Gadavist), gadoterate (Dotarem), gadoteridol (ProHance) [9,10] (Table 1). Macrocyclic GBCAs are round-shape structures which are more stable than linear ones because they have lower dissociation constants [9,23,71].

Nevertheless, both linear and macrocyclic GBCAs have been used in routine clinical practice for almost 30 years with no serious adverse effects described other than nephrogenic systemic fibrosis (NSF) in patients with severe renal insufficiency [9,23,70-73]. Nowadays, there are evidence that GBCAs can cause acute adverse reactions such as allergy, hypersensitivity reactions or chemotoxic responses [6]. Furthermore, there is a possibility of very late adverse reactions of gadolinium retention in skin, brain or bones. Gadolinium retention is assessed by biopsy and tissue histological analysis. Over the last decade radiology started to play a role in detecting GBCA's accumulation in organs. The aim of this article is to assess the side effects of MRI contrast agents in various organ systems.

MATERIALS AND METHODS

The study was conducted by an electronic database subscription of Lithuanian University of Health Sciences: PubMed (Medline), EMBASE, ClinicalKey, ScienceDirect. We tried to review and summarize the published literature of GBCAs effect in various organ systems. Our research also carried out a forward citation and bibliographic search by identifying studies regarding NSF, contrast induced nephropathy (CIN), gadolinium deposition, gadolinium retention, GBCAs in the brain. We also reviewed practical recommendations, guidelines and published manuals on contrast safety.

RESULTS

Gadolinium accumulation in tissue: deposition in brain.

The incidence of GBCAs accumulation in brain tissues has risen. Especially over the

past few years, there are a number of published studies about gadolinium deposits in the brain [5,6,10-24,26-35,42,44,46,48-50,52-55,59,62-69].

Nowadays there are radiological diagnostic possibilities to diagnose tissue accumulation of GBCAs. Gadolinium retention in the brain was already detected in regions of increased signal intensity in the deep brain nuclei on unenhanced T1-weighted MR-images [6,11,23]. The association between these appearances and GBCAs were noted first in 2015. High levels of gadolinium in four regions of the brain of patients who had 4 or more contrast-enhanced MRI's were detected [9,11]. Inductively coupled plasma mass spectrometry (ICP-MS) and electron probe microanalysis helped to determine gadolinium accumulation in post-mortem brain tissues of patients who were exposed to intravenous GBCAs and did not have a renal disease [9,11]. Unenhanced T1-weighted MR signal intensities were quantified from prescribed neuroanatomic regions of interest in the posterior fossa (dentate nucleus and pons) and basal ganglia (globus pallidus and pulvinar of the thalamus) (Figure 1) [11-17]. A number of published searches show that gadolinium deposion is one of differential diagnosis of T1 hypertensities in the globus pallidus and dentate nucleus [11,15,23,73,74]. However, other studies established that the signal intensity changes observed on MRI are specific to GBCAs deposition. [6,11-17]. In addition, there is a strong correlation between cumulative GBCA dose and tissue gadolinium concentration. It was believed that GBCAs do not cross an intact blood-brain barrier. However, several studies have showed that gadolinium is able to cross intact blood-brain barrier and the damage of this barrier is not necessary for tissue deposition[11]. It is still unknown what form of gadolinium is free ion of complex of GBCAs and there is no understanding of pathophysiology of GBCA retention in the brain [11,12,19]. A recent review by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) identified no adverse health effects of gadolinium retention in the brain [23,75]. The Committee recommended to suspend the marketing authorization of certain linear GBCAs because they cause a greater retention of gadolinium in the brain compared to macrocyclic GBCAs [10,20,23,73-75]. Linear structure of GBCAs is less stable than macrocyclic structure. It is believed that less stable structure may cause a greater chance of accumulation in brain tissue. Nonetheless, PRAC has recommended to dismiss four linear GBCA (dimeglumine, gadodiamide, gadopentate dimeglumine, gadoversetamide) due to their deposition in the brain [20,21]. There is recommendation that linear GBCAs should be only available for use when patient is allergic to macrocyclic GBCA or other alternatives for liver-specific agents are not allowed to use [22,23]. Most of studies suggest 4 to 6 linear GBCAs injections to see lesions in MRI [11,31]. In MRI spin-echo (SE) techniques GBCAs could be seen [14,15,30]. Nevertheless, T1-weighted gradient-echo sequences, such as fast low angle shot and magnetization-prepared rapid gradient echo (MPRAGE), T1 FLAIR show the hypertensity due to GBCAs [23,32-34]. More recent studies revealed other methods to detect GBCAs. T1 sequences for the visualization of gadolinium deposition found the difference of signal intensity ratio before and after GBCA exposures which was observed on both, SE and MPRAGE sequences [21-36]. To assess the effect of gadolinium accumulation in the global and regional brains of patients with prior exposure to linear GBCAs T1 and T2, the relaxation maps, produced by the mixed fast SE pulse sequence, was used [23]. In contrast, the $T2^*$ signal intensity was age-dependent and independent of previous GBCA administrations [23]. Recently, it has been suggested that quantitative susceptibility mapping (QSM) enables us to calculate the change of susceptibility value induced by GBCA accurately [23,73].

Gadolinium deposition causes nephrogenic systemic fibrosis.

NSF is an uncommon condition and potentially life-threatening disorder that affects people with severe chronic renal

insufficiency. NSF is characterized by widespread progressive tissue fibrosis that results from the deposition of fibroblasts and collagen [1,2,71,72]. Symptoms can appear from one day after the exposure to up 2-3 months or rarely years. The strong connection between GBCAs and developing NSF was established by the results of several studies since 2006. Furthermore, GBCAs affects skin and may cause pain, erythema or thickening of skin. Later NSF can occur in internal organs, e.g. muscle, diaphragm, liver, heart and lungs. Clinical manifestation of NSF is characterized by symmetrical skin lesions generally affecting extremities. Skin may be reddened with darkened patches, plaques. Patients may feel itchyness, burning, constant pain or loss of skin flexibility. Nonetheless, NFS can damage joints as the result of contractions. Computed tomography (CT) shows fibrosis of the fascia and muscles in the most severely affected patients. It is also seen in biopsy material after histologic examination. Several studies showed that gadolinium was found in all biopsy tissues with a very high concentration in the kidney and heart [61-64]. In one study four days before surgery patients received gadodiamide or gadoteridol during MRI . Four days later sample of bone was obtained and 4 times higher levels of gadolinium were detected in patients who had gadodiamide than those who had gadoteridol [65]. The dissociation of the gadolinium ion from its ligand in GBCAs has been proposed as a possible etiologic factor involved in the development of NSF [9,72]. It has been suggested that different GBCAs have different possibilities to cause NSF, depending on their thermodynamic stabilities and dissociation constants [36,40-44,72]. The etiology of NSF remains unclear. Patients with reduced renal function, particularly those with eGFR < 15 ml/min/1.73 m^2 or the ones on dialysis are at highest risk for NSF. Gadodiamide, gadopentate dimeglumine and gadoversetamide are the most common contrast agents to cause NSF [6,41,43]. Gadodiamide has the lowest thermodynamic stability [72]. The exposure to gadodiamide has been reported as 13 times higher compared with that of gadopentetate dimeglumine [43,72]. Gadodiamide constants and one of the highest dissociation rates compared with other GBCAs have been associated with the development of NSF [9,41-43,72].

DISCUSSION

Main studies show that T-1 weighted signal intensity changes in MRI are highly related to tissue deposition. Moreover, MRI is specific to gadolinium aggregates [52,53]. Nevertheless, studies discussed that signal intensity changes in MRI are not specific to GBCAs and may occur after manganese, iron, calcium, etc. [6,11,48]. Patients with T1 hyperintensities of dentate nucleus may have a higher possibility of Langerhans histiocytosis, multiple sclerosis, calcification, Wilson disease, neurofibromatosis, Rendu-Osler-Weber disease, manganese toxicity or other condition [26,27,28,49,50,60]

Although some acute effects of GBCAs exposure (e.g. anaphylactic and other acute reactions) have been reported, the potency for chronic and delayed manifestation of toxicity should be considered [9]. The clinical significance of deposits in brain is not yet known. Despite of data and evidence of GBCAs aggregates, the clinical significance of these changes are not known yet. Although there are studies which support the clinical impact of GBCA in brain tissue, scientists predict clinical signs of this condition. It was proposed that GBCAs may have relation with extrapyramidal system dysfunction and parkinsonism because of location of gadolinium deposits in the globus pallidus [23,45]. Likewise, patients can feel headache, bone pain and skin thickening [23,46].

NFS, unlike brain deposits, cannot be detected by MRI. The amounts deposites are small but greater than in the brain. There are studies about bone and liver retention. However, there are no clinical symptoms of accumulation in these areas [6]. GBCA exposure may cause acute pancreatitis [9]. Skin deposition causes red skin plaques

similar to those seen in NSF. There is new evidence that GBCA may aggregate in gliomas [60]. Likewise, GBCAs can cause tissue extravasation in soft tissues (Figure 2)[69].

Although gadolinium deposition is now well established to occur in patients with normal renal function, it is unclear if the gadolinium retained in tissue is in the chelated or free ion form [6,9,11,71,73-75]

There are few studies that suggest alternatives to GBCAs. The recommendations to use arterial spin labelling, an endogenous contrast. Besides, there is conception of natural D-glucose, maltitol, iron-contrast agents [23,55,56,58]. Deep learning method can be used to enhance the image quality of low-dose post-contrast enhanced images up to a level comparable with full-dose post-contrast enhanced images [54].

There are studies with animals available that indicates linear GBCA administration to be linked to deposition in the deep cerebellar nuclei of rats [23,66,67]. That was measured by MRI and correlated with ICP-MS. Few studies published about the difference in gadolinium deposition between linear and macrocyclic GBCAs. Healthy rats' heads were examined. They were exposed to linear and macrocyclic GBCAs. Both studies revealed increased signal on T1-weighted images on brain MRI in rats exposed to linear GBCAs but not in those exposed to macrocyclic GBCAs [23,66,67].

GBCAs can affect tissues in organ systems. It can cause NSF, gadolinium deposits in brain and etc. Linear gadolinium-based contrast agents contribute more to the deposits in body than macrocyclic. Gadolinium based contrast agents should be under strict regulation just like other pharmaceuticals for their adverse effects and damage of organs structures. Therefore, these agents should be strictly monitored and reviewed case by case before administration to patients to avoid gadolinium accumulation in tissues and possible diseases. According to the current data, neurologists should order contrast-enhanced MRI only after careful consideration of benefits and risks. Moreover, radiologists should give preference to macrocyclic agents, as these agents seem to be less prone to accumulate in the cerebral grey matter and have a better safety profile [49].

Table 1: FDA approved GBCAs

Brand name	Generic name	Structure
Ablavar	Gadofosveset trisodium	Linear
Dotarem	Gadoterate meglumine	Macrocyclic
Eovist	Gadoxetate disodium	Linear
Gadavist	Gadobutrol	Macrocyclic
Magnevist	Gadopentate dimeglumine	Linear
MultiHance	Gadobenate dimeglumine	Linear
Omniscan	Gadodiamide	Linear
OptiMARK	Gadoversatamide	Linear
ProHance	Gadoteridol	Macrocyclic

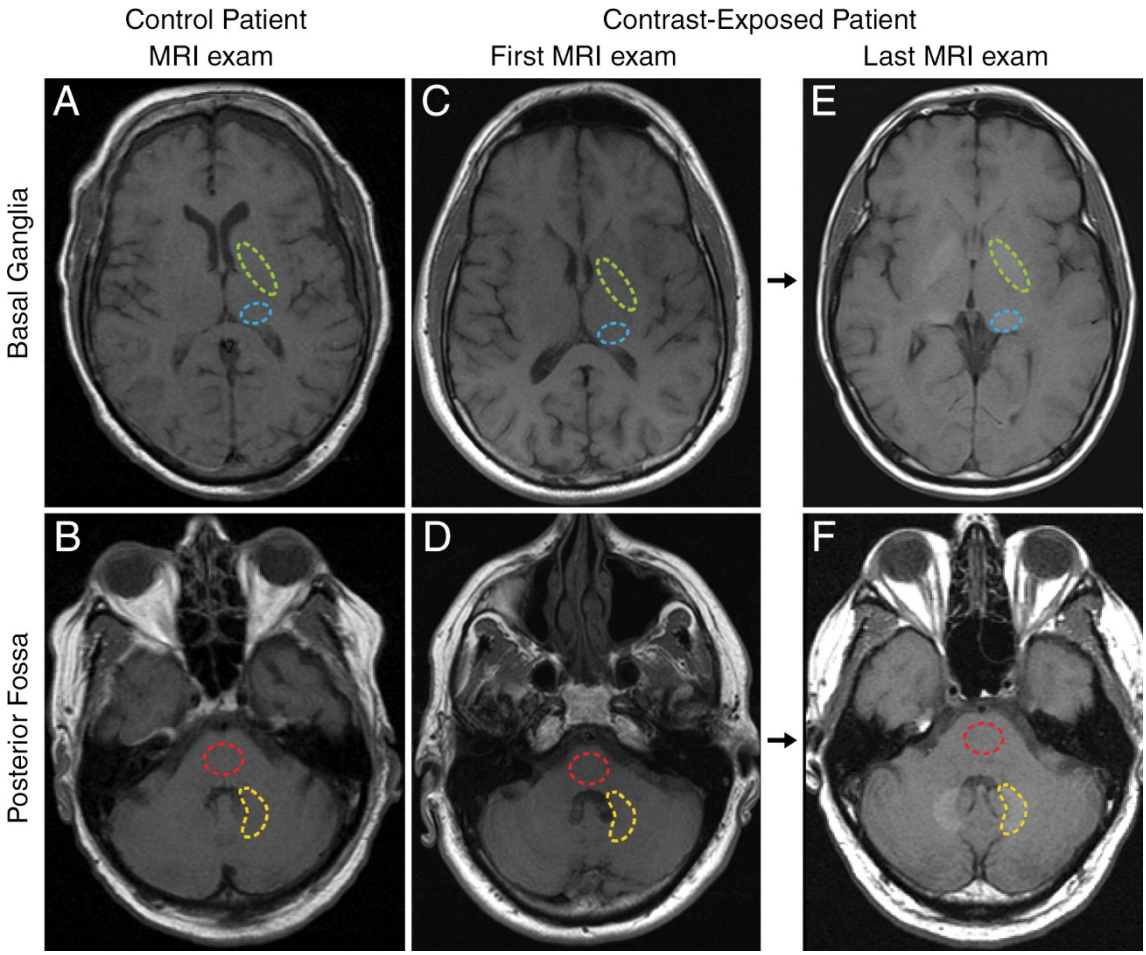

Figure 1: Axial T1-weighted MR images through, *A, C, E,* basal ganglia and, *B, D, F,* posterior fossa at level of dentate nucleus. Images are shown for, *A, B*, control group patient 4, and the, *C, D*, first and, *E, F*, last examinations performed in contrast group patient 13. Regions of interest used in quantification of signal intensity are shown as dashed lines for globus pallidus (green), thalamus (blue), dentate nucleus (yellow), and pons (red).
(McDonald RJ, McDonald JS, Kallmes DF, Jentoft ME, Murray DL, Thielen KR, Williamson EE, Eckel LJ. Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging. Radiology. 2015; 275(3): 772-82)

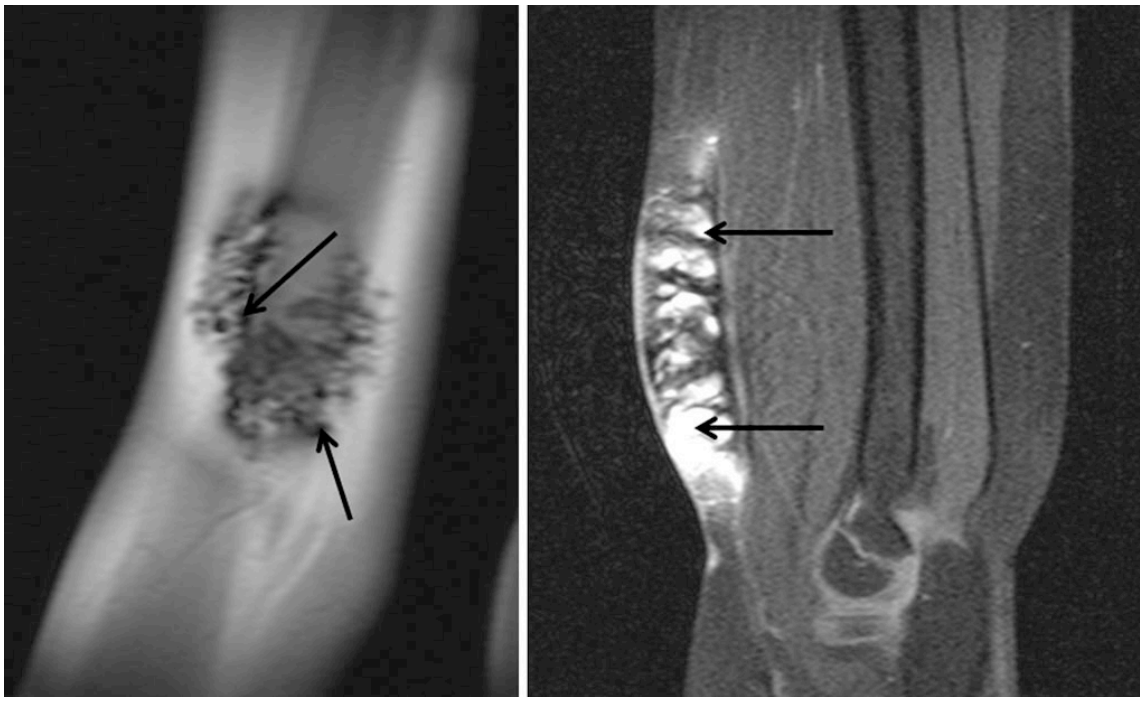

Fig. 2 Extravasation of a gadolinium-based contrast medium in the elbow region during cerebral MR. Six mL were given by automated injector, and the examination was of adequate quality, On the T1 weighted image (left), the extravasated contrast medium (black arrows) appears black due to the T2 effect of this very concentrated contrast medium, the image on the right is a T1 weighted image with longer TE than the left image, and with fat suppression. The contrast medium appears bright (black arrows) and is seen to be superficial (Thomsen Henrik S. and Judith A. W. Webb. Contrast Media Safety Issues and ESUR Guidelines, 3rd ed. Berlin, Heidelberg: Springer Berlin Heidenberg. 2014.)

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