van der Molen, AJ. Gadolinium Deposition in the Brain and Body. *Journal of the Belgian Society of Radiology.* 2019; 103(1): 71, 1–5. DOI: https://doi.org/10.5334/jbsr.1945

SHORT ABSTRACT

Gadolinium Deposition in the Brain and Body

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Keywords: Contrast Media; Gadolinium; Gadolinium Deposition; Magnetic Resonance Imaging; Brain; Bone; Skin

Gadolinium Deposition in the Brain

Clinical studies

In 2014, it was suggested that the retrospectively observed hyperintensity of the dentate nucleus and the globus pallidus relative to the pons (dentate nucleus to pons [DNP] ratio) on unenhanced T1-weighted images of a population of patients with brain tumours was related to repeated administrations of linear Gadolinium-Based Contrast Agents (GBCAs) [1]. Almost simultaneously, another group reported similar findings on unenhanced T1-weighted brain images after multiple injections of gadodiamide in patients with multiple sclerosis and patients with brain metastases [2].

After these initial reports, a multitude of retrospective studies have found increased SI ratios in the dentate nucleus and or globus pallidus for linear GBCA. No such increases were found for macrocyclic GBCA, even after large doses [3–5]. In a recent systematic review of these studies by the ESMRMB Gadolinium Research and Education Committee (ESMRMB-GREC) it was shown that there was large variety in sequence type and evaluation methodologies [6].

One of the biggest problems is that increased SI ratios at unenhanced T_1-weighted MRI are a poor biomarker for gadolinium deposition, as SI ratios do not have a linear relationship with Gd concentration, and are highly dependent on the magnetic resonance imaging (MRI) parameters used during acquisition. Absolute signal intensity in MRI depends on many MRI parameters such as field strength, sequence type/parameters, coil sensitivity/filling factor, coil tuning/matching drift, etc. Because little is known about which forms of gadolinium are present (speciation), signal intensities, or changes thereof, will not reflect true changes in gadolinium content [6, 7].

Preclinical studies

In post-mortem human brain samples, gadolinium was shown to be deposited in neuronal tissue after intravenous GBCA administration [8].

Preclinical studies in rat brains have highlighted the importance of in vivo dechelation of Gd^{3+} ions from less stable GBCAs, regardless of the presence of a renal dysfunction and with a clear dose-effect relationship. All quantities were in the nmol/g tissue range. They have also shown that differences exist in the amount of total gadolinium retained in the brain when comparing different GBCA compounds [9–12].

To date, it is unclear what forms are responsible for the increased T_1w signal increase (gadolinium speciation). Recently, it was shown that for gadolinium in the rat brain three different chemical forms have to be distinguished: intact chelate, gadolinium bound to macromolecules, and insoluble gadolinium salts [13]. The intact chelates were found for both linear and macrocyclic GBCA, but the other forms only for linear GBCA. As precipitated gadolinium does not induce any MRI signal when excited, it is likely that the gadolinium bound to macromolecules is responsible for the visible T_1w hyperintensity in clinical MRI [14].

Well-conducted long-term animal studies demonstrated that for linear GBCA, a large portion of gadolinium was retained in the brain, with binding of soluble gadolinium to macromolecules. For macrocyclic GBCA, only traces of the intact chelated gadolinium were present, with complete washout in time [15, 16].

Intact GBCA does not cross the intact blood-brain barrier. It is now believed that GBCA can reach the CSF via the choroid plexus [17] and ciliary body and can reach the brain interstitium via the glympathic system along perineural sheaths and perivascular spaces of penetrating cortical arteries. GBCA distributed into the cerebrospinal fluid cavity via the glymphatic system may remain in the eye or brain tissue for a longer duration compared to the GBCA in systemic circulation. The glympathic system may be responsible for deposition in linear GBCA as well as for GBCA clearance [18, 19].

Gadolinium Deposition in the Body

Preclinical Studies

Gadolinium deposition in bone

Lanthanide metals (gadolinium, samarium, europium, and cerium) have long been known to deposit in bone tissue and have effects on osteoblasts and osteoclasts, but the exact mechanisms are not yet well understood [20].

Gadolinium deposits have been found in samples of bone tissues of humans at higher concentrations than in brain tissue after administration of linear and macrocyclic GBCA, whereby linear GBCA deposit 4 to 25 times more than macrocyclic GBCA [21–24].

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The bone residence time for macrocyclic GBCA (up to 30 days) is much shorter than for linear GBCA (up to eight years) [22, 25]. Bone may serve as a storage compartment from which Gd is later released in the body [26, 27]. It is postulated that the long-term reservoir of gadolinium in bones might implicate that some patients with high bone turnover, such as menopausal women and patients with osteoporosis, may be more vulnerable to gadolinium deposition [22].

Gadolinium deposition in skin

Gadolinium depositions in skin have been demonstrated ever since the association of GBCA with nephrogenic systemic fibrosis in 2006. In skin biopsies of NSF patients, gadolinium was found along collagen bundles but also as insoluble apatite-like deposits, suggesting dechelation [26–29]. After linear GBCA, gadolinium deposits were found up to 40–180 times more frequently than after macrocyclic GBCA, histologic changes are more extensive, and also products of dechelation of GBCA can be found [23, 30].

Recently, gadolinium has also been found in the skin of patients with normal renal function after high cumulative GBCA doses [31]. With normal renal function, even a case of 'gadolinium-associated plaques' has been described, which suggest that gadolinium deposition in the skin after linear GBCA might give clinically relevant symptoms [32].

Gadolinium deposition in other organs

Thus far, very little is published about the effects of gadolinium deposition in other organs.

In a clinical study in the liver, gadolinium deposits have been associated with iron overload in the livers of paediatric stem cell transplantation patients with normal renal function, reacting well to iron dechelation therapy [33].

Based on animal studies, it has been suggested that residual Gd is also present in tissues samples of kidney, liver, spleen, and testis [23, 34–38]. While deposition in the brain was only 2 to 7 μg Gd, the amounts in other organs varied 168 to 2134 μg Gd for kidney, 16 to 388 μg Gd for liver, and 18 to 354 μg Gd for spleen, all per gram of tissue. In all tissues the level was highest for the linear GBCA gadodiamide [35].

Self-reported clinical symptoms

Thus far, gadolinium deposition has not been associated with clinical symptoms.

Online gadolinium toxicity support groups in the USA have claimed that their members have manifested symptoms analogous to NSF and have prolonged excretion of Gd in urine following administration of GBCA. Surveys have shown variable symptoms that occur either directly or within six weeks of GBCA administration. Most frequently reported symptoms are a burning sensation and bone pain in lower arms and limbs, central torso pain, headache with vision/hearing changes, and skin thickening and discoloration [39, 40].

This complex of symptoms was coined 'gadolinium deposition disease (GDD)'. The critical findings are the presence of gadolinium in the body beyond 30 days, combined with at least three of the following features, with onset after the administration of GBCA: i) central torso pain, ii) headache and clouded mentation, iii) peripheral leg and arm pain, iv) peripheral leg and arm thickening and discoloration, and v) bone pain [40].

Significant differences in gadolinium levels in bone and urine have been observed between individuals experiencing symptoms and those who are not [41]. A large study with a control population found more new symptoms within 24 hours after exposure to GBCA than after unenhanced MRI. From the GDD-like symptoms, only fatigue and mental confusion were more frequently reported after enhanced MRI, questioning the term GDD [42].

Gadolinium metabolism and deposition still has many knowledge gaps for which an international research agenda is important. The 2018 ACR/NIH/RSNA Meeting has made a good inventory of where future research should be aimed [7, 43].

The effect of NSF and the EMA ruling

In many European countries, the described association between NSF and exposure to linear GBCAs in 2006 has resulted in the fact that most hospitals switched early (from 2007) to macrocyclic GBCA use only, most often gadoterate or gadobutrol. After the series of publications describing increased signal intensities in the brain nuclei on unenhanced T1-weighted imaging after multiple linear GBCA exposures and post-mortem studies revealing the presence of small amounts of gadolinium in neural tissues, the European Medicines Agency instituted an article 31 procedure which eventually led to the withdrawal of EU market authorizations of the high-risk linear GBCA gadodiamide and gadoversetamide, as well as restrictions on the use of gadopentetate (MR arthrography only) and gadobenate (liver imaging only) [44, 45]. Therefore, for general use in MRI only macrocyclic GBCA are available, while the linear GBCA gadoxetate and gadobenate are available for liver-specific MRI.

For clinical practice, there are several recent guidelines to refer to [46–49].

Competing Interests

Author is member of the ESUR Contrast Media Safety Committee and member of the ESMRMB-GREC committee. No grants, support, or stocks received for the JBSR 2019 meeting.

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How to cite this article: van der Molen, AJ. Gadolinium Deposition in the Brain and Body. *Journal of the Belgian Society of Radiology*. 2019; 103(1): 71, 1–5. DOI: https://doi.org/10.5334/jbsr.1945

Submitted: 10 September 2019 **Accepted:** 29 September 2019 **Published:** 16 November 2019

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