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EDITORIAL

The Effects of Gadolinium-Based Contrast Agents on the Cerebellum: from Basic Research to Neurological Practice and from Pregnancy to Adulthood

Winda Ariyani[1] · Miski Aghnia Khairinisa[1] · Gaetano Perrotta[2] · Mario Manto[3,4] · Noriyuki Koibuchi[1]

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Abstract
Gadolinium (Gd)-based contrast agents (GBCAs) are used in magnetic resonance imaging (MRI) to increase the diagnostic yield. Current reports using animal models or human subjects have shown that GBCAs may be deposited in brain including the cerebellum. Although further studies may be required to clarify the toxicity of GBCAs, we should be more cautious to use these agents particularly in patients who more likely to have repeated enhanced MRI along their lifespan. In this editorial, current studies to clarify the toxicity of GBCAs in the cerebellum are introduced.

Gadolinium (Gd)-based contrast agents (GBCAs) are used in magnetic resonance imaging (MRI) to increase the diagnostic yield. Studies using animal models have shown that GBCAs may be deposited in the brain after repeated injections [1–3]. Tissue depositions of linear GBCAs are much higher than those of macrocyclic GBCA. Among brain regions, the dentate nucleus of the cerebellum has been considered as a primary region for such deposition on the basis of human studies [4, 5]. Animal MRI studies also revealed the same phenomenon [3, 6]. Furthermore, the Gd deposition has also been observed in the cerebellar cortex [3, 7]. Gd compounds deposited in the cerebellum consist of both soluble and insoluble forms [1, 2]. Soluble form may be intact GBCA, whereas insoluble form may be Gd bound with organic or inorganic anions, although the exact chemical nature of insoluble form has not yet fully clarified. A large fraction of linear GBCAs is transformed to insoluble form and deposited in the cerebellum.

In addition to Gd deposition in the adult brain which has become a matter of concern for the clinical community, attention should also be paid for fetal GBCA deposition during pregnancy. Indeed, in recent studies using pregnant mice, Gd was deposited in the brain of dams and pups with higher concentration in the pup brain after GBCA injection [8, 9]. Higher levels of Gd deposition in the fetal brain may be due to the immaturity of the blood-brain barrier [10] and the blood-cerebrospinal fluid barrier, both of which are not fully developed in the perinatal period [6, 11].

Although the Gd toxicity on cerebellar development and function has not been demonstrated yet, recent studies have provided novel information [8, 12]. One such information is that Gd may disrupt the action of thyroid hormone (TH), which plays a critical role on cerebellar development [13]. Low dose (10^{-7} M) of gadodiamide (linear GBCA) augmented TH receptor (TR)-mediated transcription, whereas high dose (10^{-4} M) suppressed it [12]. In contrast, no significant change on TR-mediated transcription was observed by gadoterate meglumine (macrocyclic GBCA). In T_4-treated primary cerebellar culture, low dose (10^{-7} M) of gadodiamide augmented dendrite arborization of Purkinje cell (Fig. 1a), whereas high dose (10^{-4} M) suppressed it [12]. However, no significant change on dendrite arborization of Purkinje cell was observed by gadoterate meglumine. In T_3-treated primary cerebellar culture, both gadodiamide and gadoterate

Winda Ariyani and Miski Aghnia Khairinisa contributed equally to this work.

✉ Noriyuki Koibuchi
nkoibuch@gunma-u.ac.jp

[1] Department of Integrative Physiology, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan

[2] Service de Neurologie, Hôpital Erasme, 808 Route de Lennik, 1070 Bruxelles, Belgium

[3] FNRS, ULB-Erasme, 808 Route de Lennik, 1070 Bruxelles, Belgium

[4] Service des Neurosciences, UMons, 7000 Mons, Belgium

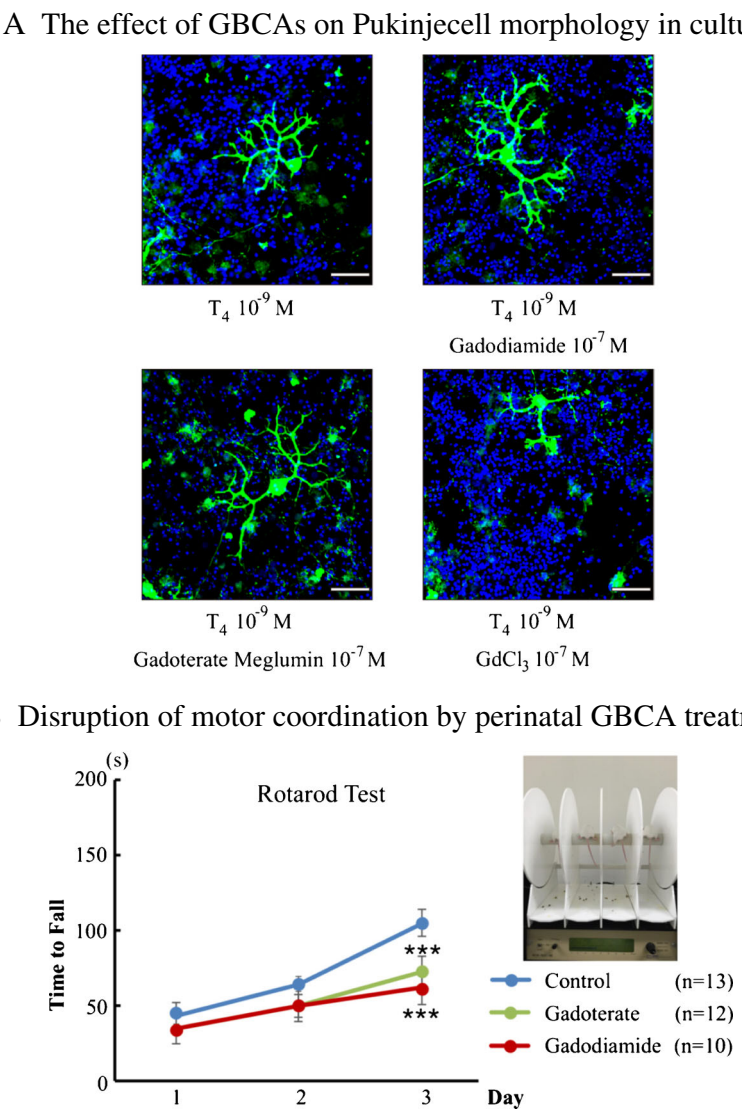

Fig. 1 **a** Representative photomicrographs showing the effects of gadodiamide (Gd-DTPA-BMA), gadoterate meglumine (Gd-DOTA), or $GdCl_3$ on Purkinje cell morphology. Bars indicate 50 μm. **b** The effect of perinatal GBCA exposure on motor coordination. Male mice (aged 70 days), whose mother received GBCA injection during gestational days 15–19, showed a significant decrease in the time spent on the rotarod on day 3 in both GBCA-treated groups (gadoterate meglumine-treated group, $p < 0.001$ and gadodiamide-treated group, $p < 0.001$, by ANOVA followed by Bonferroni test) compared with that in the control group. $^{***}p < 0.001$

meglumine suppressed the dendrite arborization of Purkinje cell and total Purkinje cell number [12]. According to previous studies, it is unlikely that GBCAs or Gd enters into the cell. Thus, Gd may not directly inhibit TR action. It may disrupt calcium signaling by blocking Ca^{2+} channel which then affects Ca^{2+}/calmodulin-dependent protein kinase type IV (CaMKIV)-mediated augmentation of TR action [14] or bind to integrin αVβ3 that is known as TH-binding site [15]. On the other hand, another in vivo study, when gadoterate meglumine or gadodiamide was intravenously injected into dams during perinatal period (embryonic day 15–19, single injection/day), which is the critical period for the functional organization of neuronal circuits, both GBCAs disrupted motor coordination and impaired memory function [8]. The magnitude of disruption was higher with gadodiamide. Motor coordination examined by rotarod was significantly disrupted (Fig. 1b), whereas memory functions examined by object recognition and object-in-location were also disrupted [8]. These behavioral alterations indicate that GBCAs affect the development of several brain regions such as the cerebellum and hippocampus. Taken together with in vitro results, GBCAs, particularly linear form, may cause toxic effects in the developing brain at least in part by disrupting the action of THs to induce behavioral alterations in mice. Therefore, GBCAs may be administered during pregnancy only when the benefit significantly outweighs the risk of exposure.

In humans, the evidence of gadolinium accumulation in brain structures after repeated administrations of GBCAs has raised important concerns about the safety of these products. Although no evidence of clinically relevant consequences has been provided to date, the scientific and medical community recommendations underline that physicians should be cautious regarding the administration of these products, especially in patients who are expected to receive several MRI scans. This is the case for both children and adults.

After (a) repeated reports of signal intensity (SI) increase in the dentate nuclei and basal ganglia on brain T1-weighted images of pediatric patients who underwent several contrast-enhanced MRI scans with administration of linear products [16–19] and (b) a study with no SI after gadobenate administration [20], an autoptic study of three children has confirmed the deposition of gadolinium in the dentate nucleus, globus pallidus, and at a smaller concentration in the thalamus and pons, after more than 3 administrations of gadodiamide, a linear GBCA [21]. Pathological changes were also observed in the dentate nuclei (gliosis, axonal spheroids). However, these signs of damage and deterioration could possibly be due to previous radiotherapy rather than the administration of GBCA. A previous single case report in a pediatric patient who received 4 administrations of a linear GBCA (gadopentetate and possibly gadodiamide) described similar observations [22]. Gadolinium deposition seems to be class-dependent, as no brain MRI modification is visible in subjects who received several doses of macrocyclic agents [18, 23–25]. Nevertheless, after an average of 10 macrocyclic GBCA administrations, a SI increase has been quantitatively measured in the dentate nucleus and globus pallidus of 50 children [26]. Anatomopathological studies after repeated macrocyclic administrations in the pediatric population are still lacking. We also miss detailed clinical/neurological reports in children exposed to GBCAs. The cerebellum of children is also in development and possible long-term impacts of gadolinium deposits on the cerebellar functions fully deserve the attention of the medical community.

First descriptions of SI increase in the cerebellum and basal ganglia were obtained from analysis of brain MRI T1-weighted images of adult patients who received more than 5 GBCA administrations [27], in comparison to subjects who underwent an equal number of unenhanced MRI scans. SI increase in adults is clearly associated to linear compound administration [28, 29].

Macrocyclic agents do not modify the signal intensity in the cerebellum and basal ganglia on MRI images [30–31], while anatomopathological findings from autoptic studies suggest that gadolinium accumulation could occur even after administration of these molecules, both in rodents and in humans [32, 33]. However, the extent of accumulation is clearly smaller with macrocyclic than with linear GBCAs [32–34], and the clinical meaning of these findings remains uncertain. In a detailed retrospective analysis of 10 patients who received an average of more than 28 doses of gadoterate, a macrocyclic agent, Perrotta et al. did not find any argument for a de novo cerebellar syndrome triggered by gadoterate [35]. In a larger retrospective study focusing on patients who underwent at least one enhanced MRI scan, no significant association was found between GBCA exposure and risk of developing movement disorders such as parkinsonian symptoms [36]. So far, no unequivocal report of neurological symptoms occurring after intracranial gadolinium accumulation has been published. Nevertheless, some functional modifications are suggested by Bauer and colleagues who showed a hypometabolism in the dentate nuclei and globi pallidi of subjects who received GBCAs when compared to naïve controls [37].

Overall, clinical consequences of gadolinium deposition in brain structures clearly need further studies evaluating prospectively motor, cognitive, and effective functions. In addition, mechanisms of gadolinium deposition and washout pathways should also be elucidated, thus providing the basis for potential therapies in case of appearance of neurological deficits, especially cerebellar ataxia. The research community should take advantage of the clinically silent phase to speed up research and set up international registries. The myriad of functions played by the cerebellum requires a specific attention by the cerebellum community and dedicated studies.

For the moment, clinicians should be cautious particularly in patients who more likely to have repeated enhanced MRI along their lifespan. The indication of GBCA administration should be systematically challenged, and the type of GBCA which will be used should be discussed. The general leading opinion is to avoid linear agents. The brain is not the sole potential target for deposits. A tissue retention occurs also in the bone, skin, and kidney. Patients with renal failure are particularly vulnerable [38]. The risk of developing nephrogenic systemic fibrosis (NSF) should be minimized to the maximum. We should also keep in mind that cerebellar patients themselves might be a vulnerable population also!

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