



Research Article

Gadolinium Brain Deposition in the globus pallidus and dentate nucleus after serial administrations of a macrocyclic gadolinium-based contrast agent in oncologic pediatric patients

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Abstract

Introduction: Gadolinium deposition in the human brain, especially in the Globus Pallidus (GP) and the Dentate Nucleus (DN) has been reported after the administration of linear Gadolinium-Based Contrast Agents (GBCAs). This study aims to determine whether repeated injections of macrocyclic GBCA are associated with an increased Signal Intensity (SI) on T1-weighted sequences in the Globus Pallidus (GP) and Dentate Nucleus (DN) in oncologic pediatric patients.

Materials and methods: This retrospective monocentric cohort study included consecutive children with at least two MRIs performed after administration of macrocyclic GBCAs. The SI measurements were determined on unenhanced T1-weighted images by drawing a circular region of interest (ROI) within GP and Thalamus (TH) and DN, Pons (P), at baseline, and at last MRI. SI ratios and the differences in ratios (GP/TH) and (DN/P) between the first and last MRI calculated.

Results: Out of 413 consecutive children attending Leon Berard cancer center, 50 patients were included, and data analysis showed significantly increased GP/TH SI ratios between the first and the last MRI ($p = 0.0305$). The DN/P SI ratios did not significantly differ between the first and the last MRI ($p = 0.2668$).

Conclusion: This study showed an increased SI in GP after several intravenous administrations of macrocyclic GBCAs but no increased SI was identified in the DN. Although no clinical adverse effects have been reported so far, the gadolinium deposits in the brain should be carefully monitored, especially in children who still undergo neurodevelopment.

Introduction

Gadolinium-Based Contrast Agents (GBCAs) have been widely used as contrast media for magnetic resonance imaging (MRI) for the diagnosis and monitoring of many diseases and an estimate of more than 300 million doses have been administered since their first use in 1988 [1-3]. Gadolinium (Gd) belongs to the family of heavy metals, free Gd is highly toxic to humans. To prevent consequences related to free Gd, GBCAs are chelated with various ligands [4-6]. In vivo, many factors such as kinetic stability, temperature, and pH can lead to the deceleration of GBCA (7,8). Despite some adverse reactions, such as rare nephrogenic systemic fibrosis, which have been reported in the past, GBCAs are considered safe [9-18]. Nowadays, the main adverse reaction risk from GBCA is an allergic reaction [16]. The seven GBCA currently available belong to two broad categories, linear and macrocyclic, which are further subdivided into ionic or nonionic agents [19]. Macrocyclic GBCAs are more stable than linear GBCAs, and ionic agents provide a more stable structure than nonionic agents [20]. Gadolinium brain deposition in patients with the normal renal function was first described in 2014 and more specifically localized in the Globus Pallidus (GP) and in the Dentate Nucleus (DN) [21,22].

To date, many studies in adults [23,24] and more rarely in children [25-28] revealed increased T1 signal intensity in the GP and DN on unenhanced T1-weighted MRI after multiple administration of linear GBCA, as supported by post-mortem studies [29-31]. After multiple administrations of macrocyclic agents, most studies reported no increased T1 signal intensity MRI in patients with normal renal function [32,33].

To our knowledge, no specific symptoms or diseases related to macrocyclic GBCA have been described. This cohort study aims to determine whether multiple injections of macrocyclic GBCA increase signal intensity on T1-weighted MRI in pediatric patients.

Material and methods

This retrospective monocentric cohort study enrolled 413 consecutive patients from 1 to 18 years, at the time of their first MRI, who was attending the Leon Berard regional cancer center in Lyon (France) between February 2011 and December 2018 for brain MRI, and who experienced at least two MRI examinations in their follow-up period with the administration of macrocyclic GBCAs were eligible for inclusion.

Exclusion criteria were patients with abnormal renal function (≥ 90 ml/min/ m²) (n=1), patients with neurofibromatosis type I (n=18), multiple sclerosis (n=2), meningo-encephalitis (n=1), patients with a history of previous use of contrast MRI for another localization (n=68), or with linear contrast agent or contrast agent type not specified (n=12), or insufficient imaging quality artifacts on MRI (n=5), lack of T1 images in the axial plane (n=168), or tumoral invasion of Regions of Interest (ROI) preventing Signal Intensity (SI) ratio determination (n=31), failure in back-up /storage of MRI on the PACS (n=57).

(Figure 1). This retrospective study received local approval from the ethics committee Lyon Sud-Est IV.

For each patient, demographic data (gender, date of birth), type of tumor, medical reason for MRI, number of MRI, date of first and last MRI, number of GBCAs administered, and history of brain radiotherapy and chemotherapy were collected [Table 1].

MRI acquisition

All MRI examinations were performed with a 1.5-T MRI (Achieva™, Philips™ Amsterdam, The Netherlands) by using a standard head matrix coil. All examinations included an unenhanced axial T1-weighted spin-echo sequence or turbo Spin echo techniques, or an unenhanced T1-weighted three-dimensional sequence. All protocols included a pre-contrast axial turbo T1-weighted sequence with the following parameters: repetition time/echo time: 513ms /10ms; section thickness: 4 mm; field of view: 240mm; matrix size: 288; flip angle: 65°.

Imaging analysis

MR images were imported on PACS (Centricity, GE Healthcare, Chicago, Illinois) and reviewed, blind with respect to clinical data, by one radiology student (J.C) and two experienced neuroradiologists working independently (5 (AMM) and 6 (AB) years experience). Each observer placed ROIs on all exams from all 50 patients.

The signal intensity was measured on unenhanced T1-weighted images by drawing a circular or ovoid Region of Interest (ROI) with a size adapted for each patient, on the right

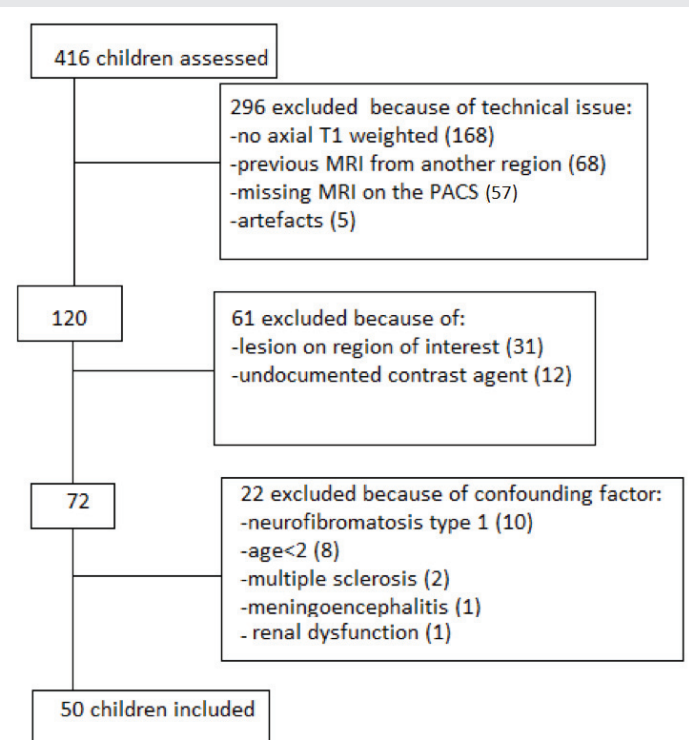


Figure 1: Flowchart of the study.



Table 1: Patient characteristics. *One patient with non-specified data at first MRI.

	Patients meeting inclusion criteria	
	N=50	
Gender		
Female	10	(20.0%)
Male	40	(80.0%)
Median age(min-max)	11.5	(3-24)
Tumor		
Acute leukemia	13	(26.0%)
Lymphoma	6	(12.0%)
Supra-tentorial embryonal tumor	5	(10.0%)
Medulloblastoma	5	(10.0%)
Glioma	14	(28.0%)
Germ cell tumor	3	(6.0%)
Craniopharyngioma	1	(2.0%)
Other types	3	(6.0%)
Macrocytic GBCA	50	(100.0%)
Total number of MRI		
2	7	(14.0%)
3	8	(16.0%)
4	3	(6.0%)
5	4	(8.0%)
6	6	(12.0%)
7	3	(6.0%)
8	1	(2.0%)
9	3	(6.0%)
10	2	(4.0%)
12	2	(4.0%)
13	1	(2.0%)
15	1	(2.0%)
16	2	(4.0%)
19	2	(4.0%)
21	1	(2.0%)
23	1	(2.0%)
28	1	(2.0%)
30	1	(2.0%)
31	1	(2.0%)
Median age (min-max) at first MRI*	7.0	(1-18)
Median age (min-max) at last MRI	8.9	(1-18)
Median delay (min-max) from first to last MRI (months)*	11.2	(0-111)
Brain radiotherapy		
No	23	(46.0%)
Yes	27	(54.0%)
Chemotherapy		
No	36	(72.0%)
Yes	14	(28.0%)

weighted images on the axial plane. If artifacts, brain lesions, or tumoral invasion prevent measurement of one of the four regions of interest to be assessed, and the corresponding ratio, only one ratio was assessed (GP/TH or DN/P) (n=17).

Statistical analysis

Patient’s characteristics are described with qualitative data expressed as n (%), and quantitative data with median (min-max).

Considering the three readers involved in measurements and repeated measurements, a general linear model was used to assess the ratio differences considering a potential patient effect.

We used a general linear model to explore the impact on the signal intensity GP/TH and DT/P ratio values at the last MRI of the potential confounding factors (gender, tumor type, age at the first MRI, number of MRI, reader, signal intensity values at the first MRI, brain radiotherapy, chemotherapy). A P value ≤0.05 was considered statistically significant.

All the analyzes were carried out with SAS software version 9.4.

side, including the Dentate Nucleus (DN), Pons (P), Globus Pallidus (GP) and Thalamus (TH), (mean diameter 4mm, range 3–9 mm) to include the anatomic structures as much as possible. The ROI was drawn without any knowledge of patient outcomes and randomly placed in each nucleus. Measures at baseline and at last MRI were performed (Figure 2A,2B). The left side was used if the right side could not be evaluated.

The ROI signal intensity ratios for the Globus Pallidus to the Thalamus (GP/TH) and Dentate Nucleus to Pons (DN/P) were calculated for all patients at baseline and at the last MRI. The differences in signal intensity ratio were calculated by subtracting from the last MRI examination the value of the signal intensity ratio of the first MRI on unenhanced T1

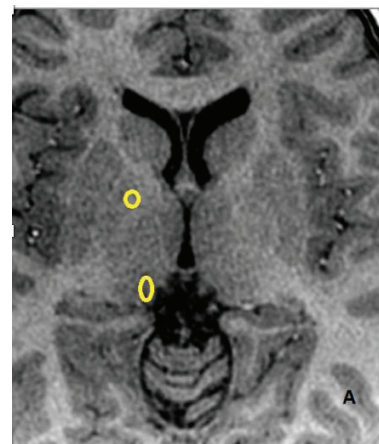


Figure 2a: Ovoid regions of interest were placed on the right side of the globus pallidus and on the right side of the thalamus.

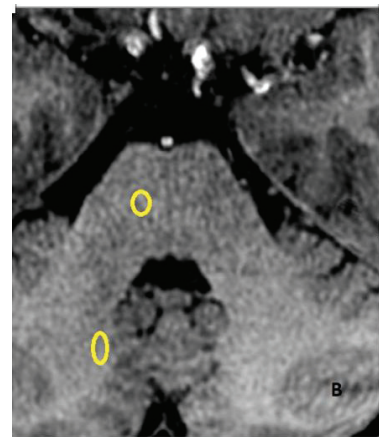


Figure 2b: Ovoid regions of interest were placed on the right side of the dentate nucleus and on the right of the pons on the right side to include as much of the anatomic structure.

Results

Population

Eligibility criteria were assessed for 416 consecutive patients, and 366 patients were excluded for technical reasons (n=296): lack of T1 images in axial plane (n=168), artifacts on MRI (n=5), previous MRI contrast agent used for another localisation (n=68), failure in MRI PACS accessing (n=57); for potential confounding factors (n=22): (abnormal renal function (n=1), neurofibromatosis type I (n=10), multiple sclerosis (n=2), meningo-encephalitis (n=1)); and for because of tumoral invasion of regions of interest preventing SI ratio determination (n=31) or undocumented contrast (n=12), the study included 50 patients (Figure 1).

40 patients were male (80%), the median age at the first MRI was 7 years (range: 1-18) and the median age at the last MRI was 8.9 years (range 1-18) (Table 1). The median number of contrast-enhanced MRIs was 6 (range 2-31). The median delay between the first and the last MRI was 11 months (range 0-111). Twenty-seven patients (54%) had brain radiotherapy and 14 patients (28%) had chemotherapy. Solid cancer or hematologic malignancies included 14 gliomas (28%), 5 medulloblastoma (13%), 13 acute leukemia (26%), 6 lymphomas (12%) and 5 medulloblastoma (10%) and 12 other types (24%). Artifacts and brain lesions, prevent to determine the DN/P SI ratio and GP/TH SI ratio between the first and last MR examination in all patients, and the DN/P SI ratio difference was determined in 47 patients and the GP/TH SI ratio was calculated in 36 patients.

Signal intensity analysis

Differences in median values of the measurements and GP/TH and DN/P signal intensity ratios, at baseline and at the last MRI were identified according to the readers.

The general linear model considering the potential impact of the three readers showed a significantly increased GP/TH signal intensity ratio between the first and the last MRI ($p=0.0305$) (Figure 3a) [Table 2a]. Conversely, no significant difference between the first and the last MRI was evidenced for the DN/P SI ratios ($p=0.2668$) (Figure 3b) [Table 2b and 3] (Figure 4). No significant difference between reader measures was found for both ratios.

Impact of some potential factors on the value of the last MRI

We tested the impact of different potential factors on the values of the last MRI and identified significant differences in the value of the first MRI, the reader, the total number of MRIs, and whether or not the patient had received brain radiotherapy [Table 4].

Discussion

Our study showed a significant increase in the signal intensity ratio of the GP/TH on unenhanced T1-weighted MRI in children after serial intravenous injection of macrocyclic GBCA. The study did not show a significant increase in signal

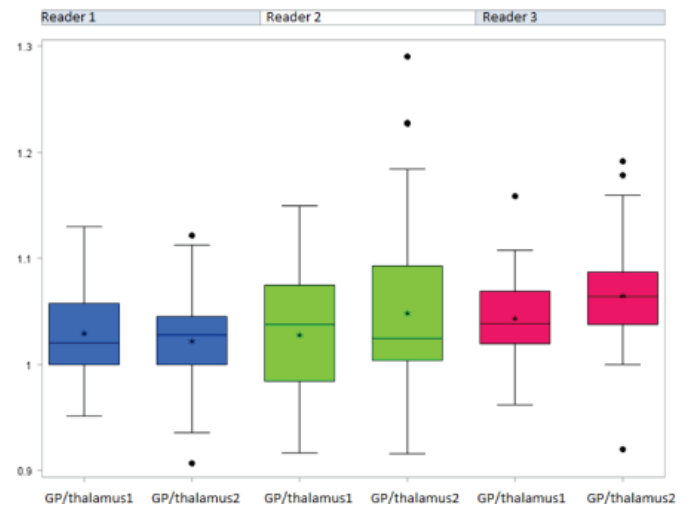


Figure 3a: Median signal intensity ratio at first and at last MRI for globus pallidus to the thalamus, according to readers #1, #2, #3.

Table 2A: Linear general model, the difference in signal intensity ratio between the first MRI and the last MRI in the globus pallidus to the thalamus.

Factor	p-value
Patient	<.0001
Reader	0.0002
MRI First-Last	0.0305
Reader*MRI First-Last	0.0511

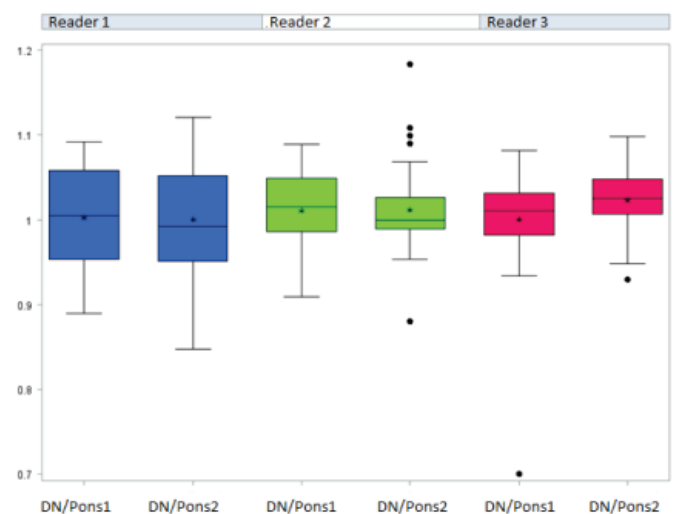


Figure 3b: Median signal intensity ratio at first and at last MRI for the dentate nucleus to pons pallidus to the thalamus, according to readers #1, #2, #3.

intensity of the DN/P ratio. Those results are contradictory to most previous studies reporting no increased signal intensity in the brain after serial injections of macrocyclic GBCAs [34,35] but increased signal intensity when linear GBCAs were used [36-38].

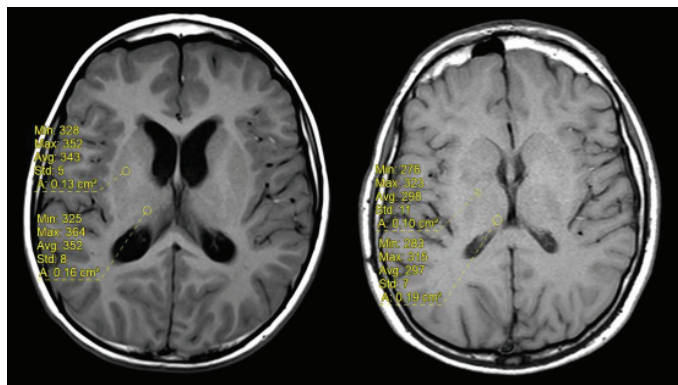
The limitations of the use of linear GBCAs are different in Europe and America. The European Medicines Agency (EMA) recommends restricting the use of linear GBCAs considering the potential associated risk of gadolinium deposition in the brain and limits the use of gadobenate dimeglumine (MultiHance®)

**Table 2B:** Linear general model, the difference in signal intensity ratio between the first MRI and the last MRI in the dentate nucleus to pons ratios.

Factor	p-value
Patient	0.0001
Reader	0.3887
MRI First-Last	0.2668
Reader*MRI First-Last	0.2732

Table 3: Impact of potential confounding factors on the globus pallidus / thalamus signal intensity ratio at last MRI.

Factor	p-value
Values at first MRI	0.0043
Reader	0.0016
Total number of MRI	0.0279
Age at first MRI	0.6595
Type of tumor	0.8551
Gender	0.4604
Brain radiotherapy	0.0124
Chemotherapy	0.4025

**Figure 4:** The ratio of GP/Thalamus for a 13 year male patient with a germ cell tumor of the pineal gland. GP/Thalamus ratio at the first MRI before injection of GBCA is an increase from 0.974 (343/352) to 1.003 (298/297) after 4 MRIs.

to hepatic uptake to visualize poorly vascularized hepatic lesions [39]. The Food and Drug Administration (FDA) does not restrict the use of linear GBCAs but **requests** health care professionals to consider the retention characteristics of each agent when selecting a GBCA for patients who may be at higher risk for gadolinium retention [40]. Rahalti et al. have shown gadolinium deposition could be avoided in patients with meningioma by using unenhanced brain MRI for follow-up scans [41].

However, Rossi Espagnet, *et al.* have shown an increased signal intensity ratio of GP/TH and DN/P after serial administrations of macrocyclic GBCA [42] and gadolinium deposits in the brain, bone, skin, and liver have been demonstrated with both linear and macrocyclic agents in autopsy studies [43] and in rodent necropsy studies [44]. The issue of gadolinium deposits in the brain has to be considered with GBCA either used as macrocyclic GBCAs or linear, even if macrocyclic GBCAs seem to be more stable than linear GBCA [45,46].

Murata, *et al.* identify deposits of gadolinium during autopsies in the brain of five patients without known blood-brain barrier abnormalities after multiple injections of macrocyclic GBCA, with concentrations detected in the globus pallidus higher than those measured in the dentate nuclei [30]. Stanescu et al. also demonstrated pediatric patients exposed to GBCAs including both macrocyclic and linear ionic agents had higher gadolinium retention in the globus pallidus [47]. Those findings may explain the increased signal intensities of GP/TH ratio in our study whereas no increase in DN/P ratio was reported.

In the current study, only children with cancer disease or hematologic malignancy were included. Patients had a brain tumor or leukemia with neurologic disorders but the region of interest was drawn on non-pathologic areas in order to avoid the blood-brain barrier rupture areas.

Patients at risk of spontaneously increased signal intensity were excluded. Indeed, T1 hyperintensity in the globus pallidus on T1-weighted images has been described in many diseases including hepatic dysfunction, neurofibromatosis type 1, hemodialysis, and abnormal renal function [47-49]. High signal intensity on T1-weighted images in the dentate nucleus can be seen in patients with Langerhans cell histiocytosis [51], multiple sclerosis [52,53] and hepatic encephalopathy [54], hemodialysis patients [55].

Clinical consequences of gadolinium retention in the brain remain unknown. No specific symptoms related to gadolinium deposition have been reported [46-57].

The dentate nucleus is predominantly used during complex motor functions, sensory functions, and cognitive tasks [58], and GP lesions may be associated with dystonia and parkinsonism [59]. Since most of our patients had significant neurological symptoms related to their pathology, the clinical consequences of gadolinium deposition were not easily assessable. Long-term longitudinal studies are required to describe the clinical significance of gadolinium deposition in the brain, particularly in the pediatric population.

The limits of our study include its retrospective design, its monocentric data collection, the reduced sample size, and the absence of a control group. Furthermore, MR imaging was acquired using various systems and scan protocols. The presence of possible confounding factors such as the history of brain radiation [60,61], or history of chemotherapy and different treatment such as surgery has to be considered. Also, we don't know how many patients received total parenteral nutrition, and parenteral nutrition can increase the signal intensity of the globus pallidus. Then four patients aged less than two years were included despite incomplete myelination [62].

Indeed, this study showed that radiation therapy, the value of the first MRI, the reader, and the total number of MRI scans were significantly associated with higher signal intensity on unenhanced T1 images on the last MRI.

**Table 4:** Results according to each reader. First and last MRI signal intensity values for GP, TH, DN, and P, and GP/TH and DN/P ratios. GP/TH: globus pallidus to thalamus; DN/P: dentate nucleus to the pons.

	Reader identification			All patient N=50
	Reader 1	Reader 2	Reader 3	
	N=50	N=50	N=50	
First MRI				
GP				
N	47	47	47	
Median (min-max)	349.0 (109-923)	351.0 (107-952)	346.9 (108-920)	349.0 (107-952)
TH				
N	47	47	47	
Median (min-max)	336.0 (108-934)	331.0 (106-975)	313.9 (106-902)	331.0 (106-975)
DN				
N	36	36	36	
Median (min-max)	318.8 (105-647)	308.0 (106-682)	304.6 (99-677)	309.0 (99-682)
Pons				
N	36	36	36	
Median (min-max)	285.1 (101-451)	290.0 (101-452)	292.7 (98-449)	287.6 (98-452)
GP/TH				
N	47	47	47	
Median (min-max)	1.02 (0.95-1.13)	1.04 (0.92-1.15)	1.04 (0.96-1.16)	1.03 (0.92-1.16)
DN/P				
N	36	36	36	
Median (min-max)	1.00 (0.89-1.09)	1.01 (0.91-1.09)	1.01 (0.70-1.08)	1.01 (0.70-1.09)
Last MRI				
GP				
N	47	47	47	
Median (min-max)	310.0 (101-446)	301.0 (103-473)	309.6 (96-464)	305.0 (96-473)
TH				
N	47	47	47	
Median (min-max)	300.0 (102-428)	291.0 (103-446)	294.6 (90-426)	294.8 (90-446)
DN				
N	36	36	36	
Median (min-max)	283.6 (96-459)	288.5 (100-458)	307.7 (91-458)	287.7 (91-459)
P				
N	36	36	36	
Median (min-max)	285.1 (101-451)	290.0 (101-452)	292.7 (98-449)	287.6 (98-452)
GP/TH				
N	47	47	47	
Median (min-max)	1.03 (0.91-1.12)	1.02 (0.92-1.29)	1.06 (0.92-1.19)	1.04 (0.91-1.29)
DN/P				
N	36	36	36	
Median (min-max)	0.99 (0.85-1.12)	1.00 (0.88-1.18)	1.03 (0.93-1.10)	1.01 (0.85-1.18)

Conclusion

Our study showed increased signal intensity, suggesting gadolinium deposit, in globus pallidus of children after multiple intravenous administration of macrocyclic GBCAs, as previously reported with linear GBCA. Despite no evidence of clinical adverse effects related to brain gadolinium deposits, such results have to be carefully considered especially in children for whom neurodevelopment may be impeded.

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