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Gadolinium deposition within the paediatric brain: no increased intrinsic T1-weighted signal intensity within the dentate nucleus following the administration of a minimum of four doses of the macrocyclic agent gadobutrol

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Abstract

Objectives—To determine whether repeated administration of the macrocyclic gadolinium-based contrast agent (GBCA) gadobutrol in children is associated with T1-weighted hyperintensity within the dentate nucleus, an imaging surrogate for gadolinium deposition.

Methods—With institutional review board approval, we identified a cohort of eight patients aged 18 years or younger who underwent at least four gadobutrol-enhanced magnetic resonance imaging (MRI) examinations of the brain from 2013 to 2017. For comparison, we identified a cohort of 19 patients who underwent at least four gadopentetate dimeglumineenhanced MRI examinations. For each examination, both dentate nuclei were contoured on unenhanced images; the mean dentate-to-pons signal intensity (DN-P SI) ratio was calculated. DN-P SI ratios from the first and last MRI exams were compared using Wilcoxon signed ranks tests and linear regression analyses.

Results—In the gadobutrol cohort, there was no significant change in the mean DN-P SI ratio from the first to the last scan (1.02 vs 1.02, $p = 1.00$). In the gadopentetate dimeglumine cohort, there was a significant increase in the mean DN-P SI ratio from the first to the last scan (1.05 vs 1.13, $p = 0.003$). After controlling for potentially confounding variables, the change in DN-P SI

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Whitney B. Pope, MD, PhD.

Conflict of interest Whitney B. Pope, MD, PhD, is a consultant for Guerbet and Bracco.

Statistics and biometry One of the authors, Hyun J. Kim, PhD, has significant statistical expertise.

Informed consent Written informed consent was waived by the institutional review board.

Ethical approval Institutional review board approval was obtained.

Methodology

- retrospective
- performed at one institution

ratio from the first to the last scan was significantly lower for patients in the gadobutrol group than in the gadopentetate dimeglumine group (β = −0.08, $p = 0.04$).

Conclusions—Repeated administration of the macrocyclic GBCA gadobutrol in children was not associated with T1-weighted dentate hyperintensity, while the repeated administration of the linear GBCA gadopentetate dimeglumine was associated with T1-weighted dentate hyperintensity, presumably due to gadolinium deposition.

Keywords

Gadolinium; Contrast media; Magnetic resonance imaging; Cerebellar nuclei; Paediatrics

Introduction

Recent studies have demonstrated the deposition of gadolinium within multiple organs in the body, including the brain, following the repeated administration of gadolinium-based contrast agents (GBCAs) for clinical magnetic resonance imaging (MRI) [1–9]. Intracranial gadolinium deposition in the brain has been associated with increased intrinsic T1weighted signal intensity, which is most detectable in the globus pallidus and the cerebellar dentate nucleus. To date, the majority of studies of intracranial gadolinium deposition have been performed in adults with few studies examining the paediatric brain.

The clinical significance, if any, of intracranial gadolinium deposition remains uncertain. However, the paediatric brain may potentially be more susceptible to deleterious effects of gadolinium deposition because the paediatric brain is generally more vulnerable to a variety of toxins [10, 11]. In addition, the lifetime dose and duration of exposure to GBCA may be greater in children than adults. For these reasons, it is important to identify the safest GBCAs for use in the paediatric population. Recent studies evaluating paediatric intracranial gadolinium deposition have focused on the linear ionic GBCA gadopentetate dimeglumine [12–15], while few studies within the paediatric population have evaluated the effect of the repeated administration of macrocyclic GBCAs. The chemical structures and trade names of commonly used linear and macrocyclic GBCAs are provided in Table 1. Radbruch et al. [16] and Ryu et al. [17] evaluated the serial administration of the macrocyclic ionic GBCA gadoterate meglumine in paediatric patients and found that this agent was not associated with T1-weighted hyperintensity within the dentate nucleus. In addition, Tibussek et al. [18] evaluated a cohort of paediatric patients who received serial administration of gadoteridol (a macrocyclic non-ionic GBCA) and gadoterate meglumine and did not find an increase in intrinsic T1-weighted hyperintensity within the dentate nucleus. Rossi Espagnet et al. [19] found that the serial administration of gadoterate meglumine was associated with increased T1-weighted hyperintensity within the dentate nucleus by quantitative region-of-interest (ROI) analysis. However, in the study by Rossi Espagnet et al. [19], there was no visible increase in T1-weighted signal intensity within the dentate nucleus [20]. The goal of this study was to determine whether repeated administration of the macrocyclic non-ionic GBCA gadobutrol in children is associated with the development of T1weighted hyperintensity within the dentate nucleus, an imaging surrogate for gadolinium deposition.

Materials and methods

Patients

With institutional review board approval for this Health Insurance Portability and Accountability Act-compliant retrospective study and a waiver of informed consent, we queried our institution's picture archiving and communication system and electronic medical record to identify all paediatric patients aged 18 years or younger without posterior fossa disease who underwent at least four gadobutrol-enhanced MRI examinations of the brain performed at our institution from 2013 to 2017 and who had not had prior exposure to any other GBCA. From this query, a total of eight patients were identified. Patients with fewer than four MRI examinations were excluded from our study, as prior studies have shown that at least four doses of gadolinium are required before progressively increased T1-weighted hyperintensity within the brain is seen [5]. For comparison, we identified a cohort of 19 patients aged 18 years or younger without posterior fossa disease who underwent at least four gadopentetate dimeglumineenhanced MRI examinations of the brain performed at our institution from 2013 to 2017. The standard paediatric dose of 0.1 mmol/kg was administered for all GBCAs.

Characteristics of the patients in our study cohort, including age, sex, diagnosis, history of chemotherapy, history of radiation, number of MRI examinations, and time interval between the first and last scans are shown in Table 2. Patient diagnoses were classified as tumoural (supratentorial glioma, ganglioglioma, craniopharyngioma, acute myeloid leukaemia, hypothalamic glioma, hypothalamic pilocytic astrocytoma, embryonal rhabdomyosarcoma, esthesioneuroblastoma, optic glioma, vestibular schwannoma, choroid plexus carcinoma, juvenile nasopharyngeal angiofibroma, lumbar ependymoma, supratentorial ependymoma, meningiomatosis, suprasellar mass, calvarial mass) and non-tumoural (demyelinating disease and intraventricular haemorrhage).

MRI examination

All MRI examinations were performed on 1.5-T (Avanto or Sonata, Siemens Medical Solutions, Erlangen, Germany; Signa HDxt, GE Medical Systems, Milwaukee, WI, USA) or 3 T scanners (TrioTim, Skyra, or Prism; Siemens Medical Solutions, Erlangen, Germany). For 18 of the 27 patients (67%), serial imaging was performed on scanners of the same magnetic field strength. Of these 18 patients, 13 (72%) had imaging performed exclusively on a 1.5-T scanner, while the other 5 patients (28%) had imaging performed exclusively on a 3-T scanner. Two unenhanced axial T1-weighted protocols were utilised. Eighty-three percent of the scans were a routine T1-weighted spin-echo sequence (slice thickness of 4 mm; TR, 398 ms; TE, 5 ms; flip angle of 90 degrees), and 17% of the scans were a magnetisation preparation rapid acquisition gradient-echo (MP-RAGE) volumetric sequence (slice thickness of 0.9 mm; TR, 1,900 ms; TE, 3 ms; flip angle of 15 degrees).

Image analysis

For each axial pre-contrast T1-weighted examination, the right and left dentate nuclei were manually contoured on a single axial slice using Vitrea (Vital Images, Minnetonka, MN, USA). We selected the dentate nucleus because it is the most commonly studied site of

progressively increasing T1weighted hyperintensity within the brain following repeated gadolinium administration. Furthermore, McDonald et al. [5] demonstrated that the dentate nuclei contained that highest median concentration of deposited gadolinium in their autopsy cohort. For each patient, the dentate nuclei were identified on later MRI examinations in which the dentate nuclei appeared relatively hyperintense compared to surrounding cerebellar tissue. This information was then used to guide the contouring of the dentate nuclei on earlier MRI examinations in which the margins of the dentate nucleus were not well delineated. Subsequently, a circular region of interest (ROI) with a diameter of 8 mm was manually placed in the central pons. The ratio of the mean signal intensity of the dentate nuclei to the mean signal intensity of the pons was calculated for each examination for each patient.

Statistical analysis

Shapiro-Wilk tests were performed to test for normality of the DN-P SI ratios. Wilcoxon signed ranks tests were performed to compare the DN-P SI ratios on the first and last scans in the gadobutrol and gadopentetate dimeglumine groups. In addition, we compared the change in the DN-P SI ratio from the first to the last MRI examination for patients in the gadobutrol group and patients in the gadopentetate dimeglumine group using Mann-Whitney tests. Ordinary least squares regression was performed to assess the effect of the type of GBCA on the change in the DN-P SI ratio while controlling for the number of doses of gadolinium received, patient age, patient diagnosis, history of chemotherapy and history of radiation. Binary variables were created for the type of GBCA (1 for gadobutrol, 0 for gadopentetate dimeglumine), patient diagnosis (1 if patient's diagnosis was tumoural, 0 if the patient's diagnosis was non-tumoural), history of chemotherapy (1 if present, 0 if not present) and history of radiation (1 if present, 0 if not present). In the ordinary least-squares regression model, the independent variable was the change in the DN-P SI ratio from the first scan to the last scan. The dependent variables in the model were the type of GBCA, number of doses of gadolinium received, patient age, patient diagnosis, history of chemotherapy and history of radiation. Additionally, for direct comparison with the eight patients in our gadobutrol cohort, we identified an age-matched subcohort of eight patients who received an equivalent number of doses of gadopentetate dimeglumine. A p value of less than 0.05 was considered to be statistically significant. Analyses were performed using SPSS 23 for Windows (IBM, Armonk, NY).

Results

Patients

Our cohort was comprised of 14 male (52%) and 13 female (48%) paediatric patients (Table 2). Within both the gadobutrol and gadopentetate dimeglumine groups, each patient received, on average, five MRI examinations. Patients in the gadobutrol group received between four and seven MRI examinations. Patients in the gadopentetate dimeglumine group received between four and five MRI examinations. Within our study cohort, 25 of the patients (93%) had brain tumours. Nine of the patients (33%) had a history of chemotherapy, and five patients (19%) had a history of radiation therapy. The time elapsed between the first

and last MRI examinations ranged from 1 month to 7 years, similar to prior studies in children with a range of 1.2–12.9 years [13].

Dentate signal intensity following repeated GBCA administration

Shapiro-Wilk tests demonstrated that the DN-P SI ratios on the first and last scans were not normally distributed ($p = 0.015$ and 0.003, respectively). Thus, Wilcoxon signed ranks tests were performed. In the gadobutrol cohort, there was no significant change in the mean DN-P SI ratio from the first to the last scan (1.02 vs 1.02, $p = 1.00$), as shown in Fig. 1. In the gadopentetate dimeglumine cohort, there was a significant increase in the mean DN-P SI ratio from the first scan to the last scan (1.05 vs 1.13, $p = 0.003$, Fig. 1). The change in the DN-P SI ratio from the first to the last scan was significantly lower in the gadobutrol cohort than in the gadopentetate dimeglumine cohort (0.00 vs 0.08, $p = 0.02$).

Furthermore, for direct comparison with the eight patients in our gadobutrol cohort, we identified an age-matched subcohort of eight patients who received an equivalent number of doses of gadopentetate dimeglumine. In both of these groups, patients received between four and seven MRI examinations with a mean of five MRI examinations. Within this age-matched and gadolinium dose-matched subcohort of eight patients who received gadopentetate dimeglumine, there was a significant increase in the mean DN-P SI ratio from the first scan to the last scan (1.02 vs 1.10, p = 0.02, Figs. 2 and 3). In these age-matched and gadolinium dose-matched subcohorts, the change in the DN-P SI ratio from the first to the last scan was significantly lower in the gadobutrol subcohort than in the gadopentetate dimeglumine subcohort (0.00 vs 0.08, p = 0.01).

In addition, we considered the possibility that changes in protocol and magnetic field strength could impact T1weighted hyperintensity. Within a subcohort of 22 patients who had the same T1-weighted protocol on the first and last scans (5 patients who received gadobutrol, 17 patients who received gadopentetate dimeglumine), we found a significant increase in the DN-P SI ratio in the gadopentetate dimeglumine group (1.04 vs 1.12, $p = 0.01$), but there was no significant change in the DN-P SI ratio in the gadobutrol group (1.01 vs 1.01, $p = 0.89$). Furthermore, within a subcohort of 16 patients who had the same MRI protocol and same magnetic field strength on the first and last scans (3 patients who received gadobutrol, 13 patients who receive gadopentetate dimeglumine), we found a significant increase in the DN-P SI ratio in the gadopentetate dimeglumine group (1.05 vs 1.12, $p = 0.046$), but there was no significant change in the DN-P SI ratio in the gadobutrol group (1.02 vs 1.03, $p = 1.00$).

Linear regression model

An ordinary least squares regression model was constructed to evaluate the effect of the type of GBCA on the change in the DN-P SI ratio while controlling for the number of doses of gadolinium received, patient age, patient diagnosis, history of chemotherapy and history of radiation. After controlling for these potentially confounding variables, the change in DN-P SI ratio from the first to the last scan was significantly lower for patients in the gadobutrol group than for patients in the gadopentetate dimeglumine group [β (regression coefficient for the type of GBCA binary variable) = −0.08, $p = 0.047$]. After controlling for these other

variables, patients in the gadobutrol group had a change in the DN-P SI ratio that was, on average, 0.08 less than patients in the gadopentetate dimeglumine group.

Discussion

In this study, we sought to determine whether repeated administration of the macrocyclic GBCA gadobutrol in children (who received a minimum of four doses) is associated with the development of T1-weighted hyperintensity within the cerebellar dentate nucleus, an imaging surrogate for gadolinium deposition. We found that in paediatric patients who received repeated administrations of gadobutrol, there was no significant change in the mean DN-P SI ratio from the first to the last scan. However, in paediatric patients who received repeated administrations of the linear GBCA gadopentetate dimeglumine, there was a significant increase in the mean DN-P SI ratio from the first to the last scan, consistent with prior published studies in both children and adults [4; 8; 1214]. There was a visible increase in T1-weighted dentate signal intensity following the serial administration of gadopentetate dimeglumine, but not following the serial administration of gadobutrol. A linear regression model demonstrated that even after controlling for the number of doses of gadolinium received, patient age, patient diagnosis, history of chemotherapy and history of radiation, the change in DN-P SI ratio from the first to the last scan was significantly lower for patients in the gadobutrol group than for patients in the gadopentetate dimeglumine group, indicating that the macrocyclic GBCA gadobutrol may be less likely to deposit within the dentate nucleus in comparison to the linear GBCA gadopentetate dimeglumine. Alternatively, it is also possible that gadobutrol may deposit within the dentate nucleus but results in less T1 shortening than gadopentetate dimeglumine.

Our findings are consistent with multiple published studies demonstrating intracranial gadolinium deposition in adults following the serial administration of linear GBCAs [1–9], including gadopentetate dimeglumine [1; 4; 8]. Our findings are also consistent with prior published studies in adults demonstrating that the macrocyclic GBCAs gadoteridol, gadoterate meglumine and gadobutrol may be less likely to deposit within the brain in comparison to the linear GBCA gadopentetate dimeglumine [4, 8, 21]. Stojanov et al. [22] raised the possibility of deposition with gadobutrol. They found T1-weighted hyperintensity within the dentate nucleus by quantitative ROI analysis following the serial administration of gadobutrol [22]; however, there was no convincing visible increase in T1-weighted dentate signal intensity [23].

Additionally, our findings are consistent with recently published studies in paediatric patients which found an association between serial administration of the linear agent gadopentetate dimeglumine and T1-weighted hyperintensity in the dentate nuclei [12–14]. Our results are also consistent with the recent study by Renz et al. [24], which was performed concurrently with our study. Similar to our study, Renz et al [24]. found that serial administrations of gadobutrol in children was not associated with T1-weighted dentate hyperintensity. One important difference between our study and the study by Renz et al. is that their gadobutrol subcohort was comprised of 25 patients who received three or more administrations of gadobutrol, while our gadobutrol subcohort was comprised of eight patients who received four or more administrations of gadobutrol. This is comparable in size

to Renz et al.'s subgroup of 13 patients who received four or more administrations of gadobutrol.

Our results are also consistent with recent studies by Radbruch et al. [16], Ryu et al. [17] and Tibussek et al. [18] who found that the serial administration of the macrocyclic GBCAs gadoterate meglumine and gadoteridol in paediatric patients was not associated with T1-weighted hyperintensity in the dentate nuclei. However, the lack of association between serial gadoterate meglumine administration in paediatric patients and intrinsic T1-weighted dentate hyperintensity has recently been called into question, as Rossi Espagnet et al. [19] found that the serial administration of gadoterate meglumine was associated with increased T1-weighted hyperintensity within the dentate nucleus by quantitative ROI analysis. However, it is important to consider that in the study by Rossi Espagnet et al. there was no visible increase in the T1-weighted signal intensity within the dentate nucleus [19; 20]. In our study, we found a visible increase in dentate T1-weighted signal intensity in the gadopentetate dimeglumine subcohort, but we did not find a visible increase in dentate T1-weighted signal intensity in the gadobutrol subcohort (Fig. 3).

Our study has several potential limitations. First, this was a retrospective study, and all patients were not imaged on the same scanner with the same pre-contrast T1-weighted protocol. However, 83% of the scans were routine pre-contrast T1weighted spin-echo images of the brain. Furthermore, we normalised the dentate signal intensity to the signal intensity of the pons, which should limit the effects of scanner variability (specifically variability in field strength) and protocol variability. According to Ramalho et al. [25], the effect of magnetic field strength on the quantitative and qualitative evaluation of T1-weighted signal intensity in the dentate nucleus or other brain structures is currently unknown, and no current studies have addressed this issue. To account for the possibility that T1-weighted signal intensity may differ between 1.5 and 3 T, we identified a subcohort of 16 patients who had the same MRI protocol and same magnetic field strength on the first and last scans, and the results were similar. In this subcohort, we found a significant increase in the DN-P SI ratio in the gadopentetate dimeglumine group, but there was no significant change in the DN-P SI ratio in the gadobutrol group.

Second, T1-weighted hyperintensity of the dentate nucleus was used as a surrogate for gadolinium deposition. While the direct measurement of gadolinium within cerebellar tissue would be preferable, this is much more difficult to acquire. The generation of T1-weighted hyperintensity may depend on a variety of factors which could potentially vary between contrast agents and may therefore be an imperfect measure of gadolinium brain concentration. A quantitative method based on susceptibility mapping has been utilised by other groups [26].

Third, our study did not include an age-matched control cohort of patients who did not receive any GBCA. However, by following each patient serially over time, each patient served as his or her own internal control. Fourth, patients in our gadobutrol subcohort received, on average, five doses of gadobutrol. Thus, we cannot exclude the possibility that intrinsic T1-weighted dentate hyperintensity may appear after more than five doses of gadobutrol in children. However, McDonald et al. [5] found that in adults, progressively

increased T1-weighted hyperintensity within the brain is typically seen after four doses of GBCA.

Fifth, paediatric brains may evolve over time, and changes in the DN-P SI ratio may occur as a result of normal brain development. Prior studies have shown that there may be an inverse correlation between age and the DN-P SI ratio, suggesting that without exposure to GBCAs, the DN-P SI ratio may decrease with age [27]. Therefore, a stable DN-P SI ratio across serial MRI examinations may, in fact, reflect gadolinium deposition within the dentate. Despite these limitations, our results suggest that in the paediatric patients, the macrocyclic GBCA gadobutrol may be less likely to deposit within dentate nucleus in comparison to linear GBCAs, such as gadopentetate dimeglumine.

In summary, our study contributes to the body of data demonstrating that the repeated administration of the macrocyclic GBCA gadobutrol in paediatric patients is not associated with T1-weighted hyperintensity in the dentate nucleus. Thus, the macrocyclic GBCA gadobutrol may be less likely than linear GBCAs, such as gadopentetate dimeglumine, to deposit within the paediatric brain, consistent with prior published studies in adults [4, 8, 21].

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Abbreviations

DN-P SI	Dentate-to-pons signal intensity
GBCA	Gadolinium-based contrast agent
MP-RAGE	Magnetisation preparation rapid acquisition gradient-echo

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Key Points

- Gadolinium-based contrast agents are routinely used in magnetic resonance imaging.
- Repeated administration of the macrocyclic agent gadobutrol in children was not associated with T1-weighted dentate hyperintensity.

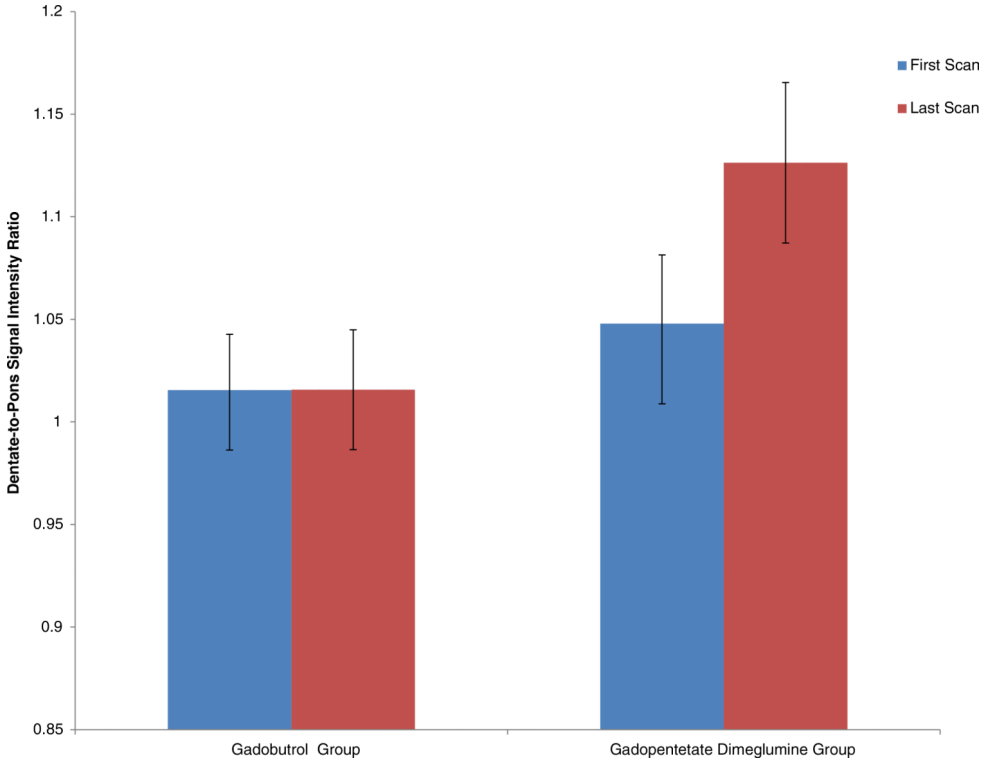

Fig. 1.

Dentate-to-pons signal intensity ratios on the first and last scans for patients in the gadobutrol ($n = 8$) and gadopentetate dimeglumine ($n = 19$) groups. In both groups, the patients received, on average, five MRI examinations. Data are the means. *Errors bars* represent 95% confidence intervals

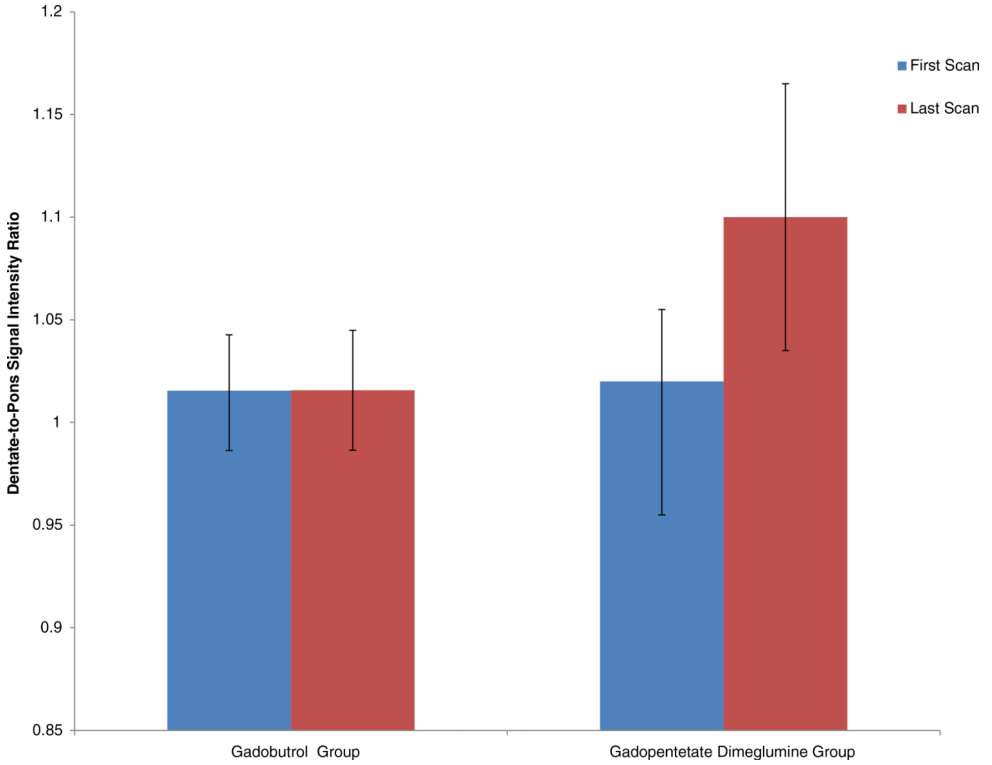

Fig. 2.

Dentate-to-pons signal intensity ratios on the first and last scans for patients in the gadobutrol subcohort ($n = 8$) and an age-matched and gadoliniumdose-matched subcohort of patients who received gadopentetate dimeglumine ($n = 8$). In each group, patients received between four and seven MRI examinations with amean of five MRI examinations. Data are the means. *Errors bars* represent 95% confidence intervals

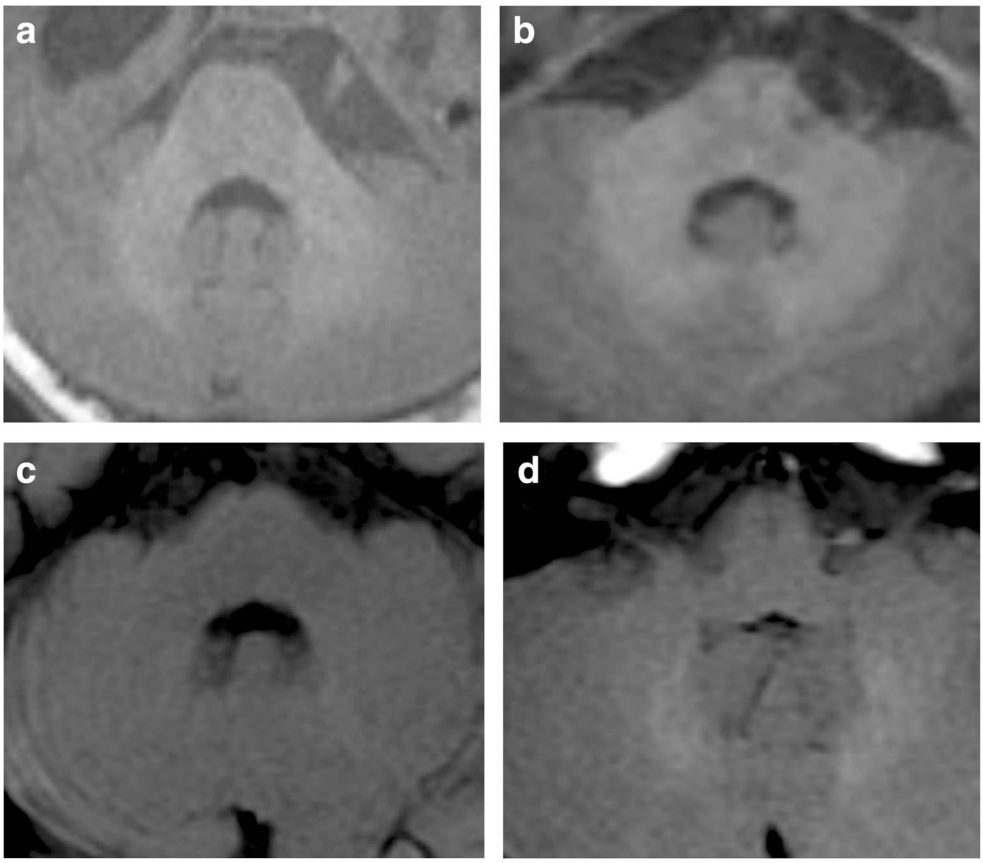

Fig. 3.

Dentate signal intensity in a patient in the gadobutrol group and in a patient in the gadopentetate dimeglumine group. a, b A 1-year-old boy with choroid plexus carcinoma, who received seven gadobutrolenhanced MRI examinations. a Axial T1-weighted image on the first MRI examination. b Axial T1-weighted image on the seventh MRI examination. c, d A 1-year-old boy with embryonal rhabomyosarcoma, who received seven gadopentetate dimeglumine-enhanced MRI examinations. c Axial T1weighted image on the first MRI examination. d Axial T1weighted image on the seventh MRI examination

Table 1

Commonly used gadolinium-based contrast agents

Chemical name	Trade name	Chemical structure
Gadobutrol	Gadavist	Macrocyclic, non-ionic
Gadoteridol	ProHance	Macrocyclic, non-ionic
Gadoterate meglumine	Dotarem	Macrocyclic, ionic
Gadopentetate dimeglumine	Magnevist	Linear, ionic
Gadobenate dimeglumine	MultiHance	Linear, ionic
Gadodiamide	Omniscan	Linear, non-ionic
Gadoversetamide	OptiMARK	Linear, non-ionic

Table 2

Patient characteristics

Parameter	All patients (*n* = 27 patients)	Gadobutrol subcohort (*n* = 8 patients)	Gadopentetate dimeglumine subcohort (*n* = 19 patients)
Sex			
Male	14 (52%)	5 (62.5%)	9 (47%)
Female	13 (48%)	3 (37.5%)	10 (53%)
Age at first scan (years)[a]	8.5 (0.1–18.1)	11.7 (0.1–18.1)	7.3 (0.3–14.4)
Number of scans[a]	5 (4–7)	5 (4–7)	5 (4–5)
Interval between first and last scans (years)[a]	2.8 (0.1–7.0)	0.9 (0.1–2.3)	3.6 (1.0–7.0)
History of chemotherapy	9 (33%)	1 (12.5%)	8 (42%)
History of radiation	5 (19%)	1 (12.5%)	4 (21%)
Diagnosis			
Tumour	25 (93%)	7 (87.5%)	18 (95%)
Other[b]	2 (7%)	1 (12.5%)	1 (5%)

Data are means with percentages in *parentheses* unless otherwise indicated

[a] Data are the ranges

[b] Other diagnoses include demyelinating disease and intraventricular haemorrhage