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Gadolinium deposition in the paediatric brain: T1-weighted hyperintensity within the dentate nucleus following repeated gadolinium-based contrast agent administration

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AIM: To determine whether repeated gadolinium-based contrast agent administration (GBCA) in children is associated with the development of increased T1-weighted signal intensity within the cerebellar dentate nucleus.

MATERIALS AND METHODS: With institutional review board approval for this The Health Insurance Portability and Accountability Act-compliant retrospective study, a cohort of 41 patients under the age of 18 years who underwent at least four contrast-enhanced magnetic resonance imaging (MR) examinations of the brain from 2005 to 2015 were identified. For each examination, both dentate nuclei were manually contoured, and the mean dentate nucleus-to-pons signal intensity (DN-P SI) ratio was calculated. The DN-P SI ratios from the last to first MRI examination were compared, and the correlation between DN-P SI ratio and cumulative gadolinium dose was calculated using a linear mixed effect model to control for potentially confounding variables.

RESULTS: For the 41 patients in the cohort, there was a significant increase in the mean DN-P SI ratio from the first MRI to the last MRI examination (1.05 versus 1.11, p=0.004). After controlling for patient diagnosis, history of chemotherapy or radiation, sex, and age, there was a significant positive association between DN-P SI ratio and cumulative gadolinium dose (coefficient=0.401, p=0.032).

CONCLUSION: Repeated GBCA administration in children is associated with increased T1-weighted signal intensity within the dentate nucleus.

Introduction

It has recently been demonstrated that gadolinium-based contrast agent (GBCA) administration for clinical magnetic resonance imaging (MRI) can result in gadolinium

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deposition or retention in multiple organs, including the brain.[1–11] Gadolinium deposition in the brain is associated with increased intrinsic signal intensity on T1-weighted images, which is most detectable in the globus pallidus and the cerebellar dentate nucleus. To date, most studies of brain gadolinium retention have been performed in adults with few studies of the paediatric brain. Although the clinical significance, if any, of brain gadolinium deposition or retention is uncertain, the paediatric brain could be more susceptible to the deleterious effects of gadolinium deposition because the paediatric brain is in general more vulnerable to a variety of toxins.[12,13] Additionally, the lifetime dose and duration of exposure to GBCA may be greater in children than adults. Initial studies documenting intracranial gadolinium deposition in adults focused on linear contrast agents, such as gadopentetate dimeglumine and gadodiamide.[2,4] Subsequent studies in adults have suggested that macrocyclic gadolinium-based contrast agents, such as gadoteridol and gadoterate meglumine, may be less likely to deposit within the brain in comparison to gadopentetate dimeglumine[3,6]; however, Stojanov *et al.* found that the macrocyclic agent gadobutrol was associated with increasing T1-weighted hyperintensity within the dentate nucleus and globus pallidus.[9] Thus, the nature of deposition of macrocyclic versus linear agents is currently unclear. Three recently published studies examining gadolinium deposition within the paediatric brain have focused exclusively on the linear agent gadopentetate dimeglumine.[14–16]

Gadolinium-enhanced MRI is an essential component of neuroimaging and clinical care in paediatric and adult patient populations. Thus, the aim of the present study was to investigate whether, as with adults, the paediatric brain shows imaging evidence of gadolinium retention following repeated exposure to a variety of GBCA.

Materials and methods

Patients

With institutional review board approval for this HIPAA (Health Insurance Portability and Accountability Act)-compliant study and a waiver of informed consent, the institution's PACS (picture archiving and communication system) was queried to identify all patients under the age of 18 years who underwent a contrast-enhanced MRI of the brain performed at between the years of 2005 and 2015. From this query, a total of 247 patients were identified. Patients with fewer than four MRI examinations, posterior fossa disease, artefacts on posterior fossa images, or incomplete contrast documentation were excluded, resulting in a study cohort of 41 patients. Patients with fewer than four MRI examinations were excluded 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.[4] The present cohort included administrations of both linear gadolinium-based contrast agents, such as gadopentetate dimeglumine, gadobenate dimeglumine, and gadodiamide, and macrocyclic agents, such as gadobutrol. The cumulative contrast dosage, as well as other clinical data, for each patient was obtained from the institution's electronic medical record. For the calculation of the cumulative contrast dosage, all gadolinium-based contrast-enhanced MRI examinations performed at the authors' institution, as well as outside examinations for which contrast data was available were included Table S1. This calculation included MRI examinations of the brain, as well as any other MRI examinations that utilised GBCAs. The standard paediatric dose of 0.1 mmol/kg was administered for all GBCAs. Patient demographics, including age, sex, diagnosis, history of chemotherapy, history of radiation therapy, number of MRI examinations, and time interval between the first and last examinations are presented in Table 1. Patient diagnoses were classified as tumoural (supratentorial glioma, craniopharyngioma, lymphoma, esthesioneuroblastoma, parameningeal rhabdomyosarcoma, hypothalamic pilocytic astrocytoma, optic glioma, supratentorial germ cell tumour, and meningiomatosis) and non-tumoural conditions (autoimmune central nervous system disease, vascular malformations, focal cortical dysplasia, frontal bone osteomyelitis, and traumatic brain injury).

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 MRI systems (TrioTim, Skyra, or Prism, Siemens Medical Solutions, Erlangen, Germany). For 28 of the 41 patients (68%), serial imaging was performed on systems of the same magnetic field strength. Of these 28 patients, 23 (82%) had imaging performed exclusively on 1.5 T systems, while five of the 28 patients (18%) had imaging performed exclusively on 3 T systems. Ninety-two percent of the scans were routine axial pre-contrast T1-weighted spin-echo images of the brain, and 8% of the scans were axial pre-contrast magnetisation preparation rapid acquisition gradient-echo (MP-RAGE) volumetric images of the brain.

Table 1
Patient characteristics.

Parameter	No. of patients (n=41)
Sex (Female:Male)	16:25
Age at first scan (years)[a]	7.75±4.88
Age at last scan (years)[a]	11.51±4.67
Number of scans per patient[a]	9.27±4.23
Cumulative gadolinium dose (ml)[a]	44.47±35.07
Interval between the first and last MRI (years)[a]	3.76±2.89
History of chemotherapy	18/41
History of radiation	6/41
Diagnosis (tumour:other)[b]	36:5

[a] Data are the means±the standard deviation. The unit for cumulative gadolinium dose is millilitre equivalents at the standard concentration of GBCAs (i.e., gadopentetate dimeglumine).

[b] Other diagnoses include autoimmune central nervous system diseases, vascular malformations, focal cortical dysplasia, frontal bone osteomyelitis, and traumatic brain injury.

Image analysis

For each axial pre-contrast T1-weighted examination, one of the authors (I.O.), a paediatric neurologist who was blinded to the clinical data, manually contoured the right and left dentate nuclei on a single axial section using the Analysis of Functional NeuroImages software (AFNI, NIH-Neuroimaging Informatics Technology Initiative, Bethseda, MD, USA). The dentate nucleus was selected as this is the most commonly studied site of progressively increasing T1-weighted hyperintensity within the brain following gadolinium administration. In addition, McDonald *et al.* found that the dentate nuclei contained that highest median concentration of deposited gadolinium in their autopsy cohort.[4] 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 margin of the dentate was not well defined. In some cases, T2-weighted images were also used to help identify the dentate nuclei. Subsequently, circular region of interests (ROIs) with a diameter of 3 mm were manually placed on the right and left side of the pons on the same section on which the dentate nuclei were contoured. A neuroradiology fellow (J.R.Y.), who was also blinded to the clinical data, reviewed the contours and ROIs for appropriate placement. The mean signal intensity of the right and left dentate nucleus and the mean signal intensity of pons were calculated, and 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

The dentate nucleus-to-pons signal intensity (DN-P SI) ratio of the first MRI examination was compared with the DN-P SI ratio for the last MRI examination using paired *t*-tests. Using repeated longitudinal MRI examinations, linear mixed effect models were constructed with random intercept and slope to test the relationship between DN-P SI ratio and cumulative gadolinium dose, while controlling for patient diagnosis, history of chemotherapy or radiation, sex, and age. Spearman's correlation analyses were performed to evaluate the relationship between age and the DN-P SI ratio on the first MRI examination, prior to receiving gadolinium. *p*-Values <0.05 were considered to be statistically significant. Statistical analyses were performed using Prism 7 (Graphpad Software, La Jolla, CA, USA) and Stata 14.1 (StataCorp., College Station, TX, USA).

Results

Patients

The present cohort was comprised of 25 male (61%) and 16 female (39%) paediatric patients under the age of 18 years (Table 1). On average (±standard deviation), each patient received 9.27±4.26 MRI examinations. Thirty-five of the patients (85%) had brain tumours. Eighteen of the patients (44%) had a history of chemotherapy, and six patients (15%) had a history of irradiation.

T1-hyperintensity within the dentate nuclei following repeated GBCA administration

For the 41 patients in the cohort, there was a significant increase in the DN-P SI ratio from the first MRI to the last MRI (mean DN-P SI ratio±standard error, 1.053±0.012 versus 1.110±0.013, $p<0.001$), as shown in Figs. 1 and 2. For each patient, the DN-P SI ratio at each MRI examination is shown graphically in Fig. 3. The possibility that changes in protocol could impact T1-weighted hyperintensity was considered. Within a sub-cohort of 30 patients who had routine T1-weighted spin-echo images obtained on the initial and last MRI examinations, a significant increase in the DN-P SI ratio was found (1.055±0.014 versus 1.102±0.013, $p<0.001$). Furthermore, within a sub-cohort of 20 patients who had routine T1-weighted spin-echo images obtained on the initial and last examinations performed on a 1.5 T system, a significant increase in the DN-P SI ratio was found (1.066±0.018 versus 1.108±0.013, $p=0.001$).

Cumulative gadolinium dose and T1-hyperintensity within the dentate nuclei following repeated GBCA administration

Using a linear mixed effect model to control for patient diagnosis, history of chemotherapy or radiation, sex, and age, a significant positive association between cumulative GBCA dose and the DN-P SI ratio was found (coefficient=0.401; 95% confidence interval: 0.035–0.768; $p=0.032$). The time elapsed between the first and last studies ranged from 1 month to 11 years, similar to prior studies in children with a range of 1.2–12.9 years.[16] The mean age at the time of the first scan was 7.8 years. The mean age at the time of the last scan was 11.5 years. The present cohort included patients with both very short and very long intervals between first and last scans, and both demonstrated increased intrinsic T1-weighted signal intensity.

Age and T1-hyperintensity within the dentate nuclei prior to GBCA administration

To better understand the potential relationship between dentate T1 signal intensity and age, the association between patient age and dentate nucleus signal intensity from the first MRI for each patient, i.e., before the patient received any GBCA was analysed. In patients over the age of 1 year, there was an inverse correlation between age and the DN-P SI ratio on the first MRI prior to GBCA administration with a trend toward significance ($r=-0.298$, 95% CI: −0.593–0.066, $p=0.096$, Spearman's correlation, Fig. 4). Older children were more likely to have a lower DN-P SI ratio than younger children on their first MRI.

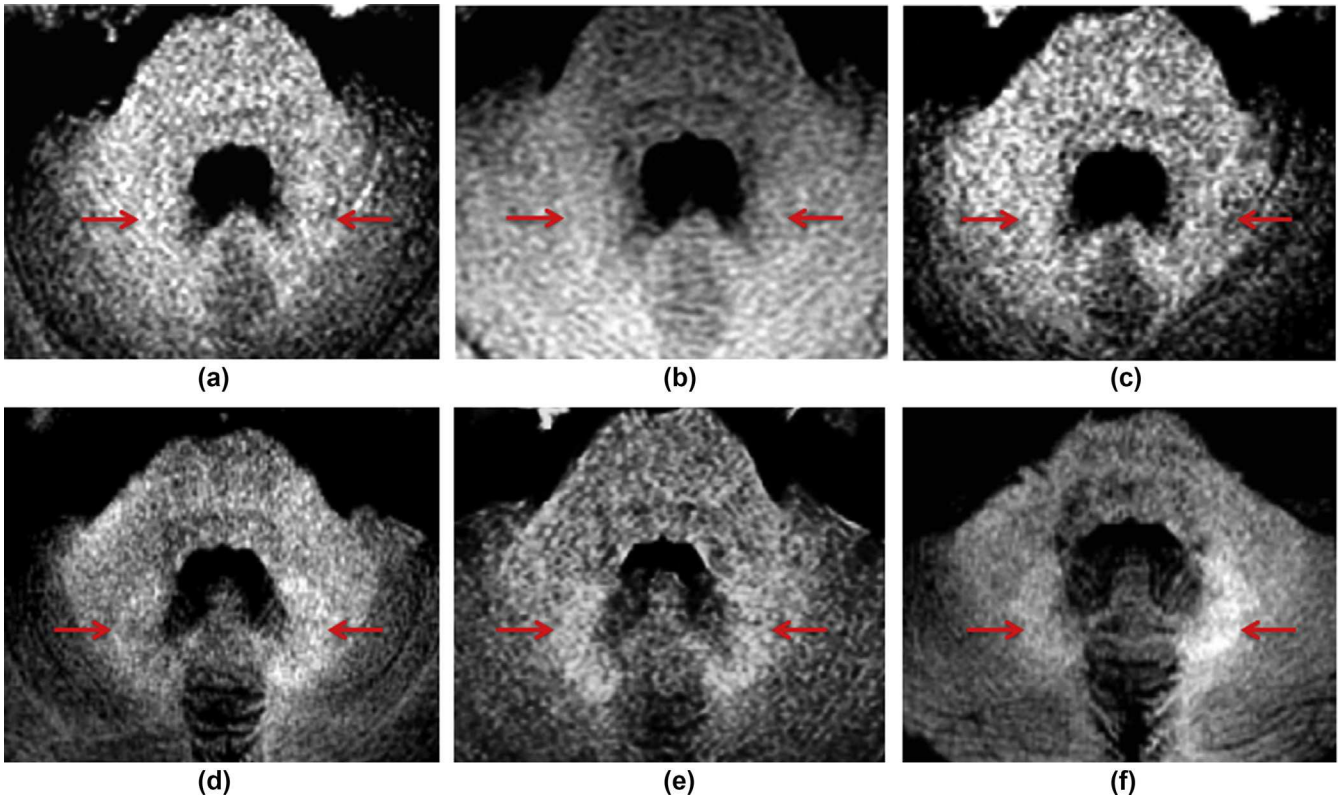

Figure 1 Increasing T1-weighted hyperintensity in the dentate nuclei following repeated GBCA administration. Axial pre-contrast T1-weighted images in a 13-year-old girl with non-Hodgkin lymphoma. She received six MRI examinations with gadopentetate dimeglumine over an 18-month period ((a–f), respectively).

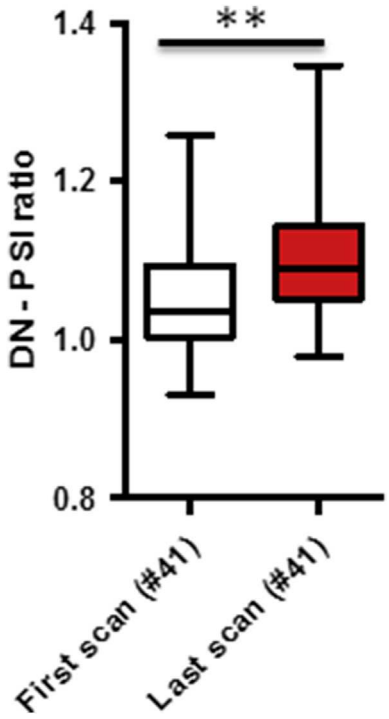

Figure 2 Distribution of DN-P SI ratios following repeated GBCA administration. Boxplots show the distribution of median, first and third quartiles, minimum, and maximum values of DN-P SI ratios. For the cohort of 41 patients, there was a significant increase in the DN-P SI ratio from the first MRI to the last MRI (p=0.004).

Discussion

The aim of the present study was to determine if T1-weighted signal intensity within the dentate nucleus increases in the paediatric brain following repeated GBCA administration, a phenomenon that has been well-documented in adults. For the cohort of 41 patients who received serial MRI examinations with GBCAs, the mean DN-P SI ratio significantly increased from the first MRI examination to the last MRI examination. A linear mixed effects model demonstrated that even after controlling for patient diagnosis, history of chemotherapy or radiation, sex, and age, there was still a significant association between cumulative gadolinium dose and the DN-P SI ratio.

In patients over the age of 1 year, an inverse correlation was found between age and the DN-P SI ratio on the first MRI prior to GBCA administration with a trend toward significance. This suggests that without exposure to intravenous GBCA, the DN-P SI ratio may decrease with age. Thus, even a stable DN-P SI ratio across serial MRI examinations may reflect gadolinium deposition or retention in the dentate nucleus.

The present findings are consistent with multiple published studies demonstrating intracranial gadolinium deposition in adults following serial GBCA administration.[1–9,11] The present findings are also consistent with recently published studies in paediatric patients performed concurrently with the present analyses.[14–16] Roberts *et al.*,

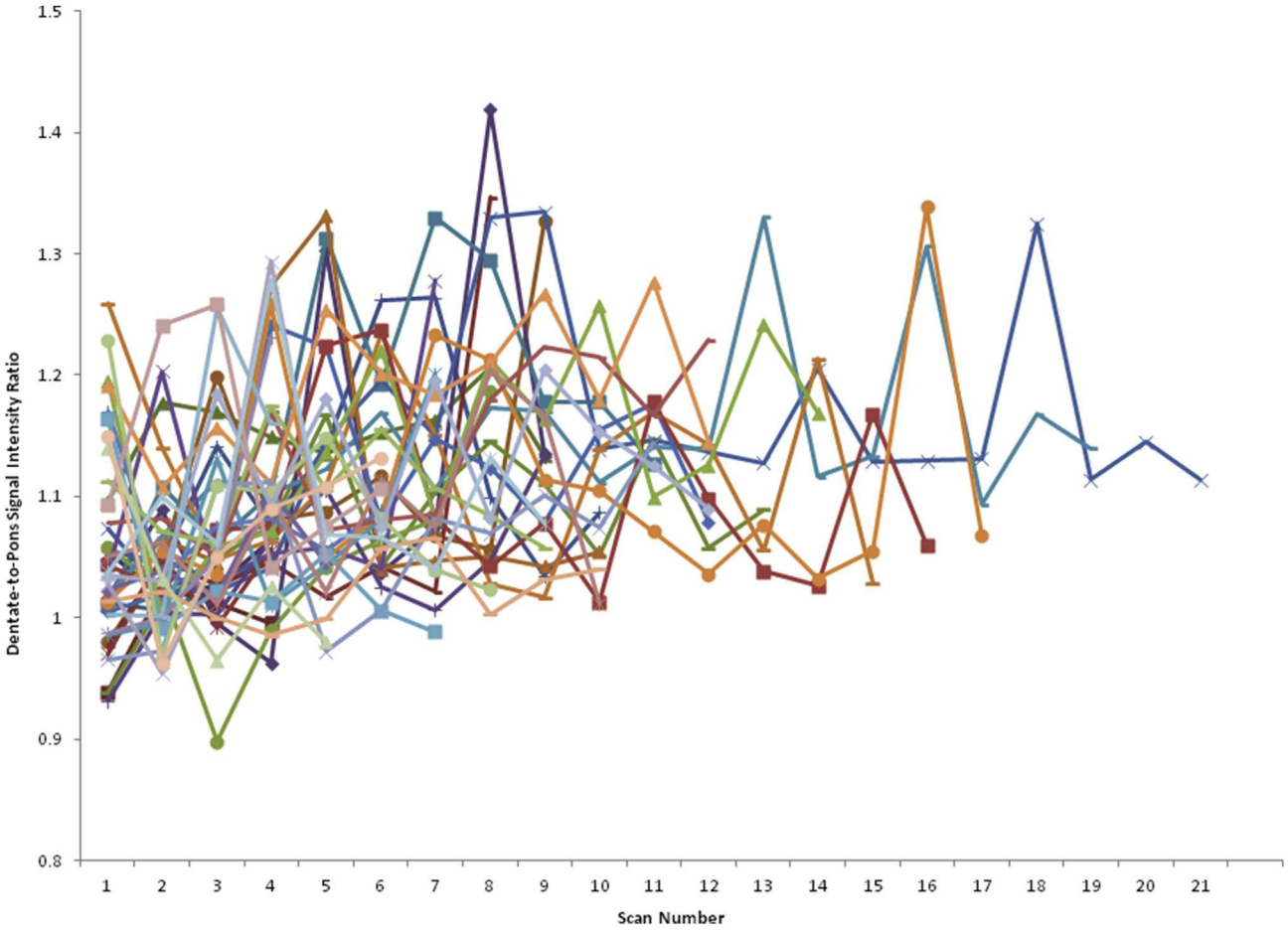

Figure 3 DN-P SI ratios following serial GBCA administrations. Each patient in the study cohort (41 patients) is represented by an individual curve.

Flood *et al.*, and Hu *et al.* found an association between serial gadopentetate dimeglumine administration in children and T1-weighted hyperintensity in the dentate nuclei.[14–16] There are some differences between the present study and these published studies. First, the present study cohort was comprised of 41 patients. Roberts *et al.* studied a cohort of 16 patients, while Flood *et al.* studied a cohort of 30 patients. Hu *et al.* studied a cohort of 21 patients. Second, the present study examined the association between the serial administration of multiple GBCAs and the DN-P SI ratio, while Roberts *et al.*, Flood *et al.*, and Hu *et al.* focused exclusively on gadopentetate dimeglumine. Third, in the present analyses, potentially confounding variables, such as patient diagnosis, history of chemotherapy, and history of irradiation, were accounted for. After controlling for patient diagnosis, history of chemotherapy or radiation, in addition to patient sex and age, a significant association between cumulative gadolinium dose and the DN-P SI ratio was found.

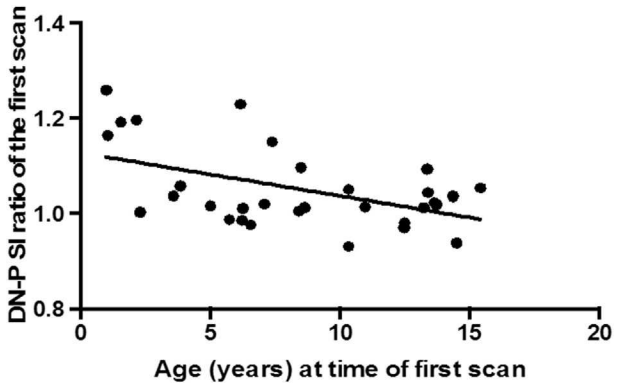

Figure 4 Scatterplot showing the association between age and DN-P SI ratio. There was an inverse correlation between age and the DN-P SI ratio on the first MRI prior to GBCA administration with a trend toward significance ($r=-0.298$, 95% CI: −0.593–0.066, $p=0.096$).

The present study has several potential limitations. First, due to the retrospective nature of this study, all patients were not imaged on the same scanner with the same pre-contrast T1-weighted protocol; however, 92% of the scans were routine pre-contrast T1-weighted spin-echo images of the brain. In addition, the dentate signal intensity was normalised to the signal intensity of the pons, which should limit the effects of scanner variability (specifically variability in field strength) and protocol variability. Second, multiple GBCA were administered to some patients, and thus the respective contributions to T1 hyperintensity in the dentate nucleus from each specific agent is difficult to

determine. Thirdly, T1 hyperintensity of the dentate nucleus was used as a surrogate for gadolinium deposition. Clearly the direct measurement of gadolinium in brain tissue would be preferable, but much more difficult to acquire. The generation of T1 hyperintensity may depend on a variety of factors, which could potentially vary between contrast agents and therefore be an imperfect measure of gadolinium brain concentration. Some studies have used a quantitative method based on susceptibility mapping.[17] Fourth, an age-matched control cohort of patients who did not receive any GBCA was not included; however, by following each patient serially over time, each patient served as his or her own internal control. Furthermore, after using a linear mixed effect model to control for patient age in addition to patient diagnosis, history of chemotherapy or radiation, and sex, a significant positive association between cumulative GBCA dose and the DN-P SI ratio was found. The results of the present study, in combination with previous reports, suggest that validation in a larger prospective trial in which all patients are imaged with a standardised pre-contrast T1-weighted protocol on the same scanner is warranted.

In summary, the present study supports the conclusion that repeated GBCA injection is associated with increased T1-weighted intensity in the paediatric brain, presumably due to gadolinium deposition or retention. In addition, without exposure to intravenous GBCA, the DN-P SI ratio may decrease with age and a stable DN-P SI ratio across serial MRI examinations could, theoretically, reflect gadolinium deposition in the dentate nucleus. Due to the retrospective nature of this study, many of the patients received both linear and macrocyclic agents, but it would be preferable to have larger cohorts that received a single GBCA only to investigate potential differences in the ability to induce T1-hyperintensity in the brain. An important caveat is that the relationship between retained gadolinium concentration and T1 hyperintensity may not be equivalent for all contrast agents. Lastly, the potential for washout of gadolinium agents over time would be of great interest, and a potential subject of future investigations.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.crad.2017.11.005.

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