MRI Brain Signal Intensity Changes of a Child During the Course of 35 Gadolinium Contrast Examinations

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We describe the observed and quantitative signal intensity changes in the brain on baseline precontrast T1-weighted MRI data of a pediatric patient who received 35 MRI examinations with gadolinium-based contrast agent (GBCA) between the ages of 8 and 20 years. The contrast agent this patient received belongs to a class of agents with linear molecular structures, which has been recently investigated in studies of gadolinium deposition in the brains of adult patients. Visual changes in signal intensity were assessed by 3 pediatric neuroradiologists, and progressive increases were the most evident in the dentate nuclei, the globus pallidus, and the thalamus. Quantitative measurements as determined from signal intensity ratios confirmed visual findings. The pattern of regional brain hyperintensity observed in this pediatric patient is consistent with findings from adult studies.

Recent reports have demonstrated qualitative and quantitative changes in the brains of adult patients, suggesting that tissue MRI gadolinium contrast deposition was the cause.[1–8] Standard MRI contrast is classified on the basis of the chemistry of the organic ligand that combines with gadolinium ion (Gd3+) to create either linear or macrocyclic MRI contrast agents. In vivo, linear agents have a much faster organic ligand-Gd3+ disassociation rate than macrocyclic agents (milliseconds/seconds vs minutes/hours). Given the recent experience with the deleterious effects of gadolinium-based MRI contrast agent (GBCA) administration in renal-impaired patients (ie, nephrogenic systemic fibrosis), there is increasing awareness of the potential toxicity of released gadolinium in its free form (Gd3+).[9] It is imperative for clinicians to develop familiarity with the potential effects and trends that have been observed in the brains of patients after multiple GBCA administrations.

Researchers from Japan and Italy first reported MRI signal intensity ratio changes in the dentate nucleus and globus pallidus of the brain in adult patients with normal renal function and that these changes were statistically correlated with the number of GBCA administrations.[1,2] Subsequently, researchers have demonstrated measureable gadolinium tissue deposition in the brains of post mortem patients, without previous history of severe renal function, who had received multiple doses of GBCAs. These groups used laboratory methods to localize, quantify, and assess the effects of gadolinium deposition in neural tissue from the dentate nuclei, pons, globus pallidus, and thalamus.[3,4] Recently, researchers from Germany compared MRI signal intensity ratios for the same previously studied brain regions in patients who had received solely linear or macrocyclic GBCAs. This report described statistically significant greater signal intensity ratios (more T1 hyperintensity) for patients who had received solely linear GBCAs compared with those who had received macrocyclic GBCAs.[5]

abstract

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Dr Miller conceptualized and designed the study, retrospectively reviewed the imaging data, and drafted the initial manuscript; Dr Hu assisted in conceptualizing and designing the study, carried out the initial data analysis, and reviewed and revised the manuscript; Ms Pokorney carried out data collection and data management, assisted in data analysis, and reviewed and revised the manuscript; Dr Cornejo retrospectively reviewed the imaging data and reviewed and revised the manuscript; Dr Towbin retrospectively reviewed the imaging data and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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In this report, we describe, the MRI changes occurring in the brain of a single pediatric patient who has received 35 GBCA doses from a linear agent when he was between the ages of 8 and 20 years. All MRI examinations were performed on 1 of 2 1.5-T magnetic resonance scanners with the same linear GBCA. The qualitative changes of this patient's brain MRI were assessed by 3 pediatric neuroradiologists and quantitative values determined by region of interest (ROI) signal intensity ratios.

CASE REPORT

Informed consent for this report was waived because of the retrospective nature of our clinical data. The patient reported is a male who was diagnosed at age 5 years (by MRI brain with contrast) with a rhabdomyosarcoma of the left orbit. After diagnosis, his care transferred from the diagnosing outside facility to our institution for treatment (surgery, chemotherapy, and external beam radiation) and subsequent surveillance. At 7 years of age, the child underwent the first of 35 contrast-enhanced MRI brain examinations at our institution. His medical history is notable for the following: at age 12, a recurrent lesion was discovered in the left orbit that was treated (surgery, chemotherapy, and external beam radiation); at age 17, a 5-mm anaplastic astrocytoma was discovered in the left thalamus and subsequently treated (surgery, chemotherapy, and proton beam therapy). At 21 years old, he has no intracranial lesion on MRI, significant visible treatment-related intracranial structural abnormality, or significant documented medical problem. No skin lesions are apparent, and renal and hepatobiliary function testing has always been normal. Recent neuropsychological testing, however, suggests difficulties with executive functioning (eg, planning, working memory, organization, and cognitive flexibility), visual memory and reasoning, reading comprehension, and math abilities.

Precontrast T1-weighted turbo-spin-echo images (repetition time: 540 milliseconds, echo time: 15 milliseconds) from this patient's 35 brain 1.5-T MRI examinations were evaluated (Philips Healthcare, Best, Netherlands). The same standard dose of (0.1 mm/kg) linear gadolinium agent (Magnevist; gadopentetate dimeglumine; Bayer HealthCare Whippany, NJ) was used for all examinations.

Retrospective review of the T1 precontrast axial MR images was performed by 3 pediatric neuroradiologists (J.M., P.C., and R.T). For each examination, reviewer consensus was achieved in the determination of the presence of hyperintensity within the thalamus, globus pallidus, caudate, dentate nuclei, and pons. For quantitative analysis, ROIs were manually drawn for the following bilateral structures for each of the 35 precontrast axial T1 images: thalamus, globus pallidus, caudate nuclei, and cerebellar dentate nuclei. Additional ROIs were drawn around the pons, corpus callosum genu, and temporalis muscle. Although previous reports have used the signal intensity ratios of the dentate nucleus to pons and the globus pallidus to the thalamus to assess GBCA accumulation,[1–4] we opted to include additional measurements from the corpus callosum genu and the temporalis muscle as the normalizing tissue signal in the computed ratios. This choice was motivated by the recent report of autopsy proven gadolinium accumulation in the pons.[3]

Statistical analysis was performed by using Stata software (Stata, version 13, College Station, TX). For each of the 35 time points, mean MRI signal intensities from the ROIs of the dentate nuclei, caudate nuclei, thalamus, and globus pallidus were normalized by the mean signal intensity of the corpus callosum genu. These ratios were then evaluated as a function of time (ie, days elapsed since first examination), and linear regression analysis was performed. The slope of the regression line for each signal intensity ratio versus time plot was tested to determine whether it was statistically significant from a value of zero. A slope of zero would have implied no effect from the consecutive GBCA injections. A value of $P < .05$ and 95% confidence intervals were used to determine statistical significance. To demonstrate that the signal intensity of the corpus callosum genu was not affected by GBCA, a ratio of the corpus callosum genu to the signal intensity of adjacent temporalis muscle was also assessed, and a regression line with a slope of zero was hypothesized.

RESULTS

The dentate nuclei, globus pallidus, and posterior thalamus showed visually evident increases in hyperintensity over the course of the multiple contrast-enhanced MRI brain examinations (Fig 1). Dentate nucleus T1 hyperintensity was visually apparent early on, beginning with the second or third MRI brain examination performed at our institution, followed by the globus pallidus and posterior thalamus, which were visible around the 13th to 15th MRI examinations. No T1 hyperintensity change was visually identified in the caudate (Fig 1) or pons. Figure 2 plots the signal intensity ratios of the globus pallidus and dentate nuclei. Note that the patient did not receive an MRI between approximately days 1000 (fifth visit) and 1750 (sixth visit). However, the normalized signal intensity ratios in the various brain regions did not decrease during this period. See Supplemental Figure 3 for similar plots in all other measured brain regions.

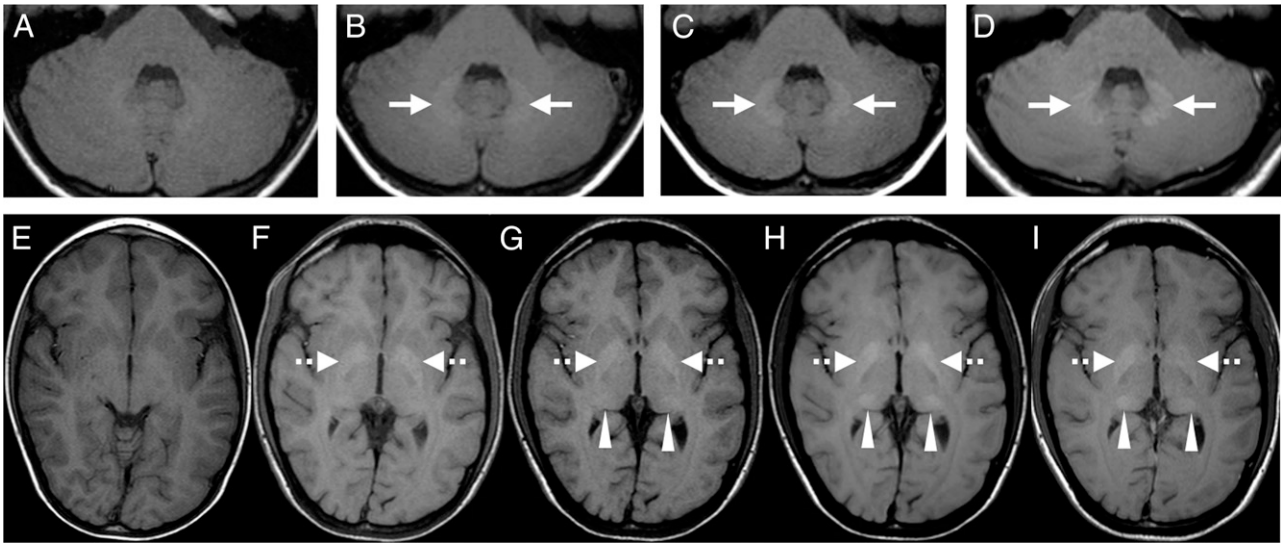

FIGURE 1

Precontrast T1 of the (A) first, (B) second, (C) third, and (D) 35th MRI showing progressive hyperintensity in the dentate nuclei (arrows). Similar images of (E) first, (F) 13th, (G) 14th, (H) 15th, and (I) 35th MRI of the globus pallidus (dotted arrows) and posterior thalamus (arrowheads).

Supplemental Table 1 summarizes the linear regression slope, coefficient of determination, and the associated 95% confidence interval between signal intensity ratios and elapsed time. The dentate nuclei exhibit the strongest positive correlation between signal intensity ratio and successive GBCA administrations (r^2 = 0.6). The next strongest correlation was found in the pons (r^2 = 0.5), followed by the thalamus (r^2 = 0.32–0.43), the globus pallidus (r^2 = 0.33–0.38), and the caudate nuclei (r^2 = 0.21–0.23). All correlations were statistically significant ($P < .05$). Note that the ratio of the corpus callosum genu to the temporalis muscle has the weakest coefficient of determination and that the 95% confidence interval includes the slope value of zero, signifying no correlation.

DISCUSSION

In this work, visually apparent and quantitatively significant changes in signal intensity were present in the brain MRIs of a pediatric patient who received 35 doses of GBCA, totaling 500 mL over 12 years. The distribution of T1 hyperintensity changes (bilateral dentate nucleus, globus pallidus, posterior thalamus) of this pediatric patient is similar to images of previous adult patients.[1–8] By studying a single subject longitudinally, potential data variability and confounding factors such as gender, comorbid conditions, and genetics were removed. With the exception of a single neurosurgical procedure to remove a 5-mm thalamic tumor, this patient's brain was otherwise free of significant iatrogenic insult. Although treatment regimens included multiple courses of chemotherapy and radiation, no visible adverse effects were demonstrated on MRI.

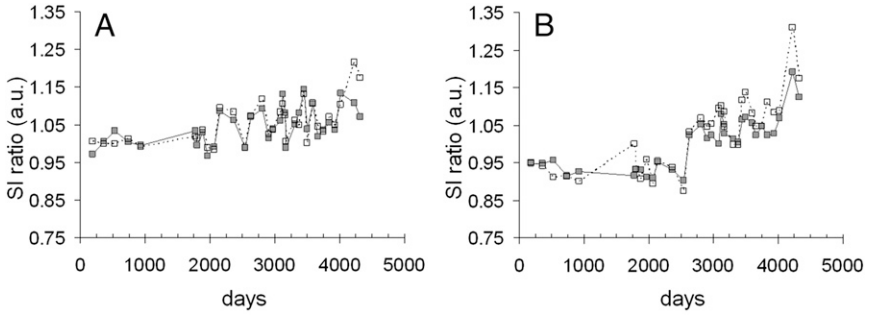

FIGURE 2

Signal intensity (SI) ratios, in arbitrary units (a.u.), measured from precontrast T1-weighted MRI are shown for the (A) globus pallidus and (B) dentate nuclei, normalized to the SI of the corpus callosum genu. Gray squares denote measurements on patient's left side; open squares denote measurements on the patient's right side.

The dominant variable factor, and most likely cause of the changes of this patient's brain MRI, was the cumulative dose of administered linear GBCA gadopentetate dimeglumine. These findings are consistent with the assertions of recent publications linking cumulative linear GBCA administrations with brain MRI changes in adult patients.[1–7] Linear GBCA deposition in the brain has been directly detected by McDonald et al[3] and Kanda et al.[4] In these studies, using inductively coupled plasma mass spectrometry, a significant correlation was exhibited between GBCA patient doses and the

amount of gadolinium deposited in the autopsied brain specimens.[3,4] Using transmission electron microscopy, the presence of gadolinium deposits within endothelial walls and neural interstitium has been demonstrated in the autopsied brains of patients exposed to GBCAs.[3] Linear GBCA deposition has also been previously demonstrated outside of the brain in human bone.[10,11] Conversely, the cumulative administrations of macrocyclic GBCA have not shown the same qualitative or quantitative findings.[5]

CONCLUSIONS

This study demonstrates the qualitative and quantitatively significant changes in signal intensity in the brain MRIs of a pediatric patient who received 35 doses of a linear intravenous GBCA. Following previous studies conducted in adults, this report demonstrates similar findings in a pediatric patient with the largest reported exposure to GBCA to date. Given this study's control for multiple possible confounding variables, the dominant variable factor, and most likely cause of the qualitative and quantitative changes of this patient's brain MRI, was the cumulative dose of administered linear GBCA gadopentetate dimeglumine.

Although there are currently a number of significant gaps in the scientific knowledge regarding the significance and possible long-term effects of intracranial GBCA deposition, serious consideration may be warranted in the selection and administration of GBCAs, especially given the theoretical[5] and observational[4] differential deposition potential of linear versus macrocyclic agents.

ABBREVIATIONS

GBCA: gadolinium-based contrast agent
Gd3+: gadolinium ion
ROI: region of interest

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