Radiology

High Signal Intensity in the Dentate Nucleus and Globus Pallidus on Unenhanced T1-weighted MR Images: Relationship with Increasing Cumulative Dose of a Gadolinium-based Contrast Material[1]

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Purpose: To explore any correlation between the number of previous gadolinium-based contrast material administrations and high signal intensity (SI) in the dentate nucleus and globus pallidus on unenhanced T1-weighted magnetic resonance (MR) images.

Materials and Methods: The institutional review board approved this study, waiving the requirement to obtain written informed consent. A group of 381 consecutive patients who had undergone brain MR imaging was identified for cross-sectional analysis. For longitudinal analysis, 19 patients who had undergone at least six contrast-enhanced examinations were compared with 16 patients who had undergone at least six unenhanced examinations. The mean SIs of the dentate nucleus, pons, globus pallidus, and thalamus were measured on unenhanced T1-weighted images. The dentate nucleus–to-pons SI ratio was calculated by dividing the SI in the dentate nucleus by that in the pons, and the globus pallidus–to-thalamus SI ratio was calculated by dividing the SI in the globus pallidus by that in the thalamus. Stepwise regression analysis was undertaken in the consecutive patient group to detect any relationship between the dentate nucleus–to-pons or globus pallidus–to-thalamus SI ratio and previous gadolinium-based contrast material administration or other factors. A random coefficient model was used to evaluate for longitudinal analysis.

Results: The dentate nucleus–to-pons SI ratio showed a significant correlation with the number of previous gadolinium-based contrast material administrations ($P < .001$; regression coefficient, 0.010; 95% confidence interval [CI]: 0.009, 0.011; standardized regression coefficient, 0.695). The globus pallidus–to-thalamus SI ratio showed a significant correlation with the number of previous gadolinium-based contrast material administrations ($P < .001$; regression coefficient, 0.004; 95% CI: 0.002, 0.006; standardized regression coefficient, 0.288), radiation therapy ($P = .009$; regression coefficient, −0.014; 95% CI: −0.025, −0.004; standardized regression coefficient, −0.151), and liver function ($P = .031$; regression coefficient, 0.023; 95% CI: 0.002, 0.044; standardized regression coefficient, 0.107). The dentate nucleus–to-pons and globus pallidus–to-thalamus SI ratios in patients who had undergone contrast-enhanced examinations were significantly greater than those of patients who had undergone unenhanced examinations ($P < .001$ for both).

Conclusion: High SI in the dentate nucleus and globus pallidus on unenhanced T1-weighted images may be a consequence of the number of previous gadolinium-based contrast material administrations.

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High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted magnetic resonance (MR) images is commonly observed. Previous studies have reported that high signal intensity in the dentate nucleus is associated with a history of brain irradiation or multiple sclerosis (1,2), whereas high signal intensity of the globus pallidus has been associated with hepatic dysfunction (3–5), Wilson disease (3,6), Rendu-Osler-Weber disease (7), manganese toxicity (8,9), calcification (8,10), hemodialysis (11), total parenteral nutrition (12), and neurofibromatosis type 1 (13). In our institution, we noticed that high signal intensity in the dentate nucleus and globus pallidus is also common in patients with a history of multiple administrations of gadolinium-based contrast material. In such patients, the signal intensity on T1-weighted images appears higher with increasing number of exposures to gadolinium-based contrast material. We hypothesized that high signal intensity of the dentate nucleus and globus pallidus on T1-weighted images was associated with previous gadolinium-based contrast material administration. The purpose of this study was to explore any correlation between the number of previous gadolinium-based contrast material administrations and high signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images.

Advance in Knowledge

- High signal intensity of both the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images correlates with the number of previous gadolinium-based contrast medium administrations (dentate nucleus: $P < .001$, regression coefficient = 0.010. 95% confidence interval [CI]: 0.009, 0.011; globus pallidus: $P < .001$, regression coefficient = 0.004, 95% CI: 0.002, 0.006).

Materials and Methods

Patients

Our institutional review board approved this study. The requirement to obtain written informed consent was waived because this was a retrospective study. All patients had given consent at the time of the examination to the use of their image data in research. We identified one patient group for cross-sectional analysis, with two subgroups for longitudinal analysis.

Cross-sectional Analysis of the Patient Group

From January 1, 2011, to February 28, 2011, 384 consecutive patients underwent brain MR imaging at our institution. Two patients did not undergo unenhanced T1-weighted imaging and were excluded from this study. One patient had a history of total parenteral nutrition containing manganese within the previous 6 months and was also excluded. The remaining 381 patients (mean age, 67.4 years; age range, 24–90 years; 229 men, 152 women) were evaluated (consecutive patient group). Most patients (377 patients) had a history of neoplastic disease, and MR imaging was performed either to evaluate tumor size or to search for new metastases. None of the patients had a history of multiple sclerosis. None of the patients had nephrogenic systemic fibrosis.

Contrast-enhanced Examination Subgroup

From the consecutive patient group, we identified 102 patients who had undergone at least six contrast material–enhanced MR examinations. Fifty-three patients were excluded because the examinations were performed before digital images were routinely stored. An additional 30 patients were excluded because they had undergone brain radiation therapy, had a brain tumor, or had abnormal liver function (see below). The remaining 19 patients were assigned to the contrast-enhanced examination subgroup (mean age, 67.7 years; age range, 51–82 years; 10 men, nine women).

Implication for Patient Care

- High signal intensity in the globus pallidus and dentate nucleus may be present on unenhanced T1-weighted MR images in patients who have undergone a relatively large number of previous gadolinium-based contrast material administrations.

Unenhanced Examination Subgroup

We identified 16 patients who had undergone at least six unenhanced examinations between May 1, 2006, and December 31, 2012 (range, 6–13 examinations; mean, 8.1 examinations). All patients had a history of lung cancer, and MR imaging was performed to detect brain metastases. None of the patients had a history of multiple sclerosis. These patients were classified as the unenhanced examination subgroup (mean age, 73.5 years; age range, 56–86 years: six men, 10 women).

Data Analysis

We evaluated the sex and age of the patients, the number and type of previous gadolinium-based contrast material administrations, whether the patients had a history of radiation therapy or chemotherapy, the site of any tumor, and the patient's hepatic and renal function. Radiation therapy was defined as a history of radiation therapy to the brain

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Abbreviations:
CI = confidence interval
eGFR = estimated glomerular filtration rate
ROI = region of interest

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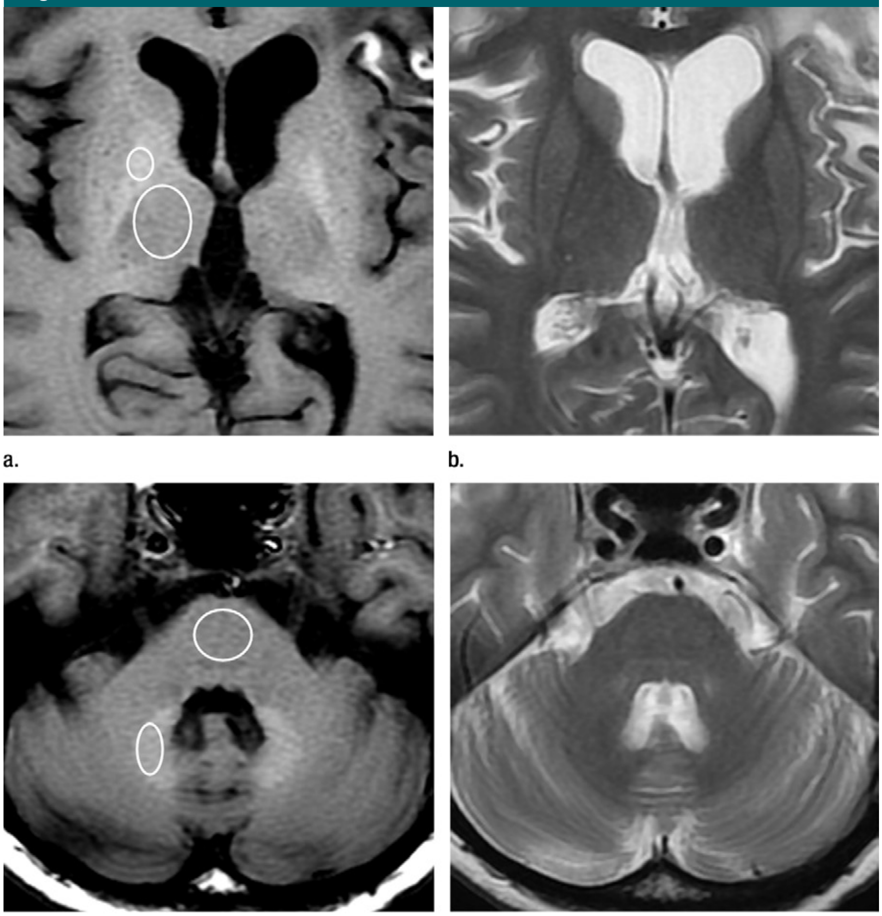
Guarantors of integrity of entire study, T.K., K.I., D.T.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, T.K.; clinical studies, T.K., H.K., D.T.; statistical analysis, T.K., K.I., K.K.; and manuscript editing, T.K., K.I., K.K., D.T.

Conflicts of interest are listed at the end of this article.

and was classified as gamma knife or other tumor-selective radiation therapy that excluded the globus pallidus and dentate nucleus from the radiation field (grade 1) or whole-brain irradiation (grade 2). A tumor was considered to be present "anywhere in body" if it was evident on the brain MR images or if a tumor had recurred anywhere in the body at a 1-year follow-up study. A brain tumor was considered to be present if primary or secondary brain tumors were detected on MR images. Patients were also grouped according to a history of chemotherapy, which was further classified according to the previous administration of molecularly targeted therapy or platinum-based chemotherapy. Abnormal liver function was defined by abnormal serum concentrations of aspartate aminotransferase, alanine aminotransferase, total bilirubin, or γ-glutamyl transpeptidase. Renal function was evaluated by calculating the estimated glomerular filtration rate (eGFR) from a recent blood sample and was classified as follows: normal (eGFR > 60 mL/min/m^2), moderately abnormal (eGFR between 30 and 60 mL/min/m^2), or severe insufficiency (eGFR < 30 mL/min/m^2). The number of previous gadolinium-based contrast material administrations was defined as the number of previous contrast-enhanced MR examinations performed at our center. At our institution, 7.5 mmol of gadopentetate dimeglumine (Magnevist; Bayer Yakuhin, Osaka, Japan) or gadodiamide (Omniscan; Daichi Sankyo, Tokyo, Japan) was used for adult patients in every contrast-enhanced MR study.

Figure 1



a. b. c. d.

Figure 1: MR images in 45-year-old woman with glioblastoma treated with surgery, chemotherapy, and radiation therapy. **(a)** Unenhanced T1-weighted image shows high-signal-intensity globus pallidus. Standard ROIs were placed around globus pallidus and thalamus. **(b)** Fast spin-echo T2-weighted image at same level as **a**. **(c)** Unenhanced T1-weighted image shows high-signal-intensity dentate nucleus. Standard ROIs were placed around dentate nucleus and pons. **(d)** Fast spin-echo T2-weighted image at same level as **c**.

Imaging and Data Analysis

Whole-brain MR imaging was performed with one of two 1.5-T MR imaging units (Signa HDxt or Signa Excite Twin Speed; GE Medical Systems, Tokyo, Japan). Axial unenhanced T1-weighted images were obtained with the following parameters: repetition time msec/echo time msec, 400–450/9; section thickness, 5 mm; number of signals acquired, two; and matrix size, 256 × 320. Axial T2-weighted images were obtained with the following parameters: 4000–5400/90; section thickness, 5 mm; number of signals acquired, two; matrix size, 256 × 320; and echo train length, 16–20.

Quantitative analysis was conducted by two radiologists (T.K. and H.K., with 10 and 4 years of experience, respectively), who were blinded to the clinical data, by using the unenhanced T1-weighted images with operator-defined region-of-interest (ROI) measurements of mean signal intensity. Oval ROIs were placed around the right dentate nucleus, central pons, right globus pallidus, and right thalamus. If the right side could not be assessed because of pulsation artifact, metal artifact, or brain necrosis, the left side was used. If the dentate nucleus, globus pallidus, or thalamus was unclear on T1-weighted images, the same section position on T2-weighted images was used to guide ROI placement. Correct ROI placement was agreed on by consensus, and ROI measurement was conducted once (see Fig 1 for examples). The dentate nucleus–to-pons signal intensity ratio was calculated by dividing the mean signal intensity of the dentate nucleus by that of the central pons. The globus pallidus–to-thalamus signal intensity ratio was calculated by dividing the mean signal intensity of the globus pallidus by that of the thalamus. The last examination of each patient from the large consecutive patient group and the first and last examinations of the contrast-enhanced and unenhanced examination subgroups were analyzed.

Statistical Analysis

Stepwise regression analysis was performed with software (PASW Statistics, version 21.0; SPSS, Chicago, Ill) to evaluate the relationships between the dentate nucleus–to-pons or globus pallidus–to-thalamus ratios and the following factors: sex, age, liver function, renal function, tumor anywhere in the body, brain tumor, number of previous gadolinium-based contrast material administrations, radiation therapy, chemotherapy, platinum-based chemotherapy, and molecularly targeted therapy.

A random coefficient model was used to evaluate changes in the dentate nucleus–to-pons or globus pallidus–to-thalamus ratios in the contrast-enhanced and unenhanced examination subgroups. The model was defined as follows: $Y_{jkl} = \beta_0 + (\beta_1 + \alpha_j)\ t_k + \beta_2\ l + \beta_3\ l\ t_k$, where Y is the signal intensity, l is the subgroup factor (contrast-enhanced examination group: $l = 0$, unenhanced examination group: $l = 1$), t_k is the time elapsed between the first and last examination (first examination: $k = 1$, last examination: $k = 2$), and β_0, β_1, β_2, and β_3 are the fixed effects and α_j is the random effect for each patient. The parameters of each model were calculated with restricted maximum likelihood. The paired t test was used to evaluate the signal changes in dentate nucleus–to-pons and globus pallidus–to-thalamus ratios in both subgroups. The random coefficient models were built and analyzed by using the R software environment for statistical computing (version 3.0.1; *http://www.r-project.org/*). $P < .05$ was considered indicative of a statistically significant difference.

Table 1

Summary of Patient Characteristics

Parameter	Consecutive Patient Group (n = 381)	Contrast-enhanced Examination Subgroup (n = 19)	Unenhanced Examination Subgroup (n = 16)
Age (y)*	67.4 ± 11.2	67.7 ± 9.6	73.5 ± 8.6
Sex			
M	229	10	6
F	152	9	10
Brain radiation therapy			
Whole brain	31	0	0
Partial or gamma knife	46	0	0
Tumor anywhere in body	222	11	9
Brain tumor	104	0	0
Chemotherapy	200	16	9
Platinum-based chemotherapy	134	11	8
Molecularly targeted therapy	48	3	3
Abnormal liver function	30	0	0
Abnormal renal function			
eGFR between 30 and 60 mL/min/m^2	36	0	3
eGFR < 30 mL/min/m^2	2	0	0

Note.—Except where indicated, data are numbers of patients.

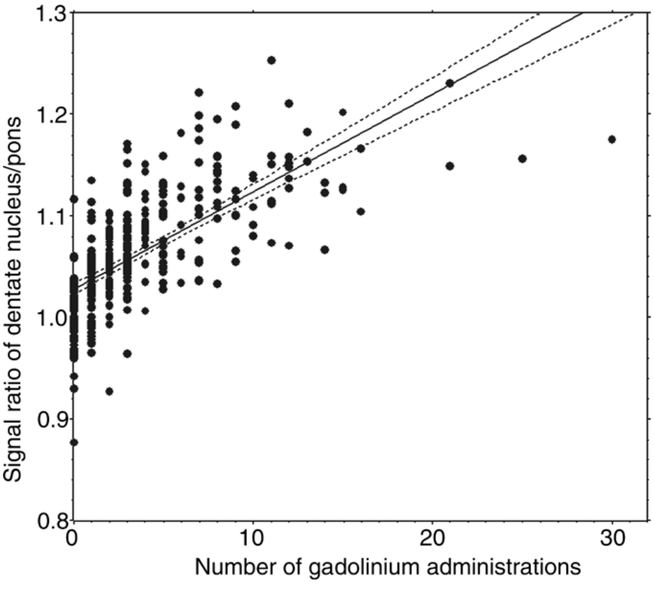
* Data are means ± standard deviations.

Results

The number of previous gadolinium-based contrast material administrations in the consecutive patient group ranged from zero to 30 (mean, 3.57). The contrast-enhanced examination subgroup had undergone six to 12 examinations (mean, 7.1 examinations). In the consecutive patient group, 31 of the 381 patients (8.1%) had undergone whole-brain irradiation, 46 (12.0%) had undergone gamma knife or other tumor-selective radiation therapy that excluded the globus pallidus and dentate nucleus from the field, 222 (58.3%) had tumors anywhere in the body, 104 (27.3%) had at least one brain tumor, 200 (52.5%) had undergone chemotherapy, 134 (35.2%) had undergone platinum-based chemotherapy, 48 (12.6%) had undergone molecularly targeted therapy, 30 (7.9%) had abnormal liver function, 36 (9.5%) had moderately abnormal renal function, and two (0.5%) had severe renal insufficiency. The characteristics of each group are outlined in Table 1.

Scatterplots of the dentate nucleus–to-pons and globus pallidus–to-thalamus ratios according to number of previous gadolinium-based contrast material administrations are shown in Figure 2 and indicate a positive correlation between the number of previous gadolinium-based contrast material administrations and the dentate nucleus–to-pons ratio. Results of stepwise regression analysis are shown in Table 2. In all steps of the stepwise regression analysis, the dentate nucleus–to-pons signal intensity ratio showed a significant correlation only with the number of previous gadolinium-based contrast material administrations ($P < .001$; regression coefficient, 0.010; 95% confidence interval [CI]: 0.009, 0.011; standardized regression coefficient, 0.695). The globus pallidus–to-thalamus signal intensity ratio showed a significant correlation with the number of previous gadolinium-based contrast material administrations in all steps of the stepwise regression analysis ($P < .001$; regression coefficient, 0.004; 95% CI: 0.002, 0.006; standardized regression coefficient, 0.288). In the final steps of the stepwise

Figure 2



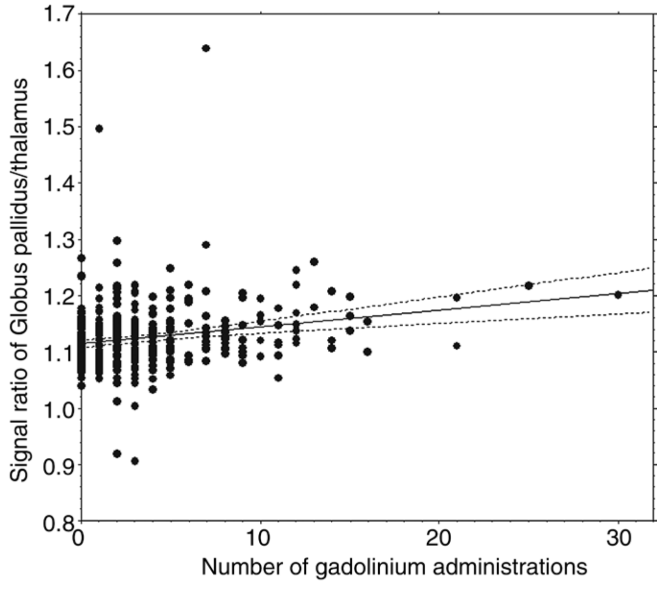


Figure 2: **(a)** Scatterplot of dentate nucleus–to-pons signal intensity ratio versus number of previous gadolinium-based contrast material administrations. **(b)** Scatterplot of globus pallidus–to-thalamus signal intensity ratio versus number of previous gadolinium-based contrast material administrations. In each plot, solid line represents linear regression and dashed lines indicate 95% confidence limits.

regression analysis, radiation therapy showed a significant negative correlation (P = .009; regression coefficient, −0.014; 95% CI: −0.025, −0.004; standardized regression coefficient, −0.151) and liver function showed a significant positive correlation (P = .031; regression coefficient, 0.023; 95% CI: 0.002, 0.044; standardized regression coefficient, 0.107) with the globus pallidus–to-thalamus signal intensity ratio. The globus pallidus–to-thalamus ratio was more strongly influenced by the number of previous gadolinium-based contrast material administrations than by radiation therapy or liver function.

Scatterplots of changes in the dentate nucleus–to-pons and globus pallidus–to-thalamus signal intensity ratio in the contrast-enhanced and unenhanced examination subgroups are shown in Figure 3. The dentate nucleus–to-pons and globus pallidus–to-thalamus signal intensity ratios in the contrast-enhanced examination subgroup exhibited increased signal intensity compared with that of the unenhanced subgroup over time. Table 3 shows the estimated fixed effects of a repeat measure linear mixed model. The time × subgroup factors of the dentate nucleus–to-pons (−0.0896; standard error, 0.0137) and globus pallidus–to-thalamus (−0.0514; standard error. 0.0097) signal intensity ratio were significant (P < .001 for both). For patients in the contrast-enhanced examination subgroup (l = 0), the coefficient of the time factor was β_1 and was 0.0874 for the dentate nucleus–to-pons signal intensity ratio and 0.0433 for the globus pallidus–to-thalamus signal intensity ratio; signal intensity increased over time. For patients in the unenhanced examination subgroup (l = 1), the coefficient of the time factor was $\beta_1 - \beta_3$ and was −0.0022 for the dentate nucleus–to-pons signal intensity ratio and −0.0081 for the globus pallidus–to-thalamus signal intensity ratio; signal intensity change was minimal.

Discussion

Our study revealed a correlation between a high-signal-intensity dentate nucleus and globus pallidus on T1-weighted images in patients with a history of gadolinium-based contrast material administration independent of renal function. To our knowledge, MR imaging findings of high signal intensity in the dentate nucleus and globus pallidus quantitatively linked to cumulative gadolinium dose have not been reported. The present findings can be added to the differential diagnosis of a high-signal-intensity dentate nucleus and globus pallidus, and some differential diagnosis may be changed.

High signal intensity of the dentate nucleus on T1-weighted images has been reported in patients with a history of brain irradiation (1) and multiple sclerosis (2). Kasahara et al (1) reported that a high-signal-intensity dentate nucleus on unenhanced T1-weighted images was associated with a history of brain irradiation. No such correlation was found in our data, whereas a correlation between high signal intensity of the dentate nucleus and the number of previous gadolinium-based contrast material administrations was noted. Patients with multiple sclerosis and those who undergo brain irradiation tend to

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Table 2

Correlations of Dependent Variables to Dentate Nucleus–to-Pons and Globus Pallidus–to-Thalamus Signal Intensity Ratios in 381 Patients

Parameter	Regression Coefficient	95% CI	Standardized Regression Coefficient	*P* Value
Analysis for dentate nucleus–to-pons ratio				
First step of analysis				
Sex	−0.007	−0.015, 0.002	−0.057	.145
Age	−0.000	0.000, 0.000	−0.004	.921
No. of previous contrast material administrations	0.009	0.008, 0.011	0.671	<.001
Brain radiation therapy	0.000	−0.010, 0.010	0.001	.990
Tumor anywhere in body	−0.007	−0.017, 0.004	−0.060	.200
Brain tumor	0.000	−0.013, 0.014	0.004	.942
Chemotherapy	0.006	−0.008, 0.019	0.050	.416
Abnormal liver function	0.003	−0.010, 0.016	0.024	.678
Platinum-based chemotherapy	0.007	−0.008, 0.022	0.040	.376
Molecularly targeted therapy	0.000	−0.016, 0.015	−0.001	.980
Abnormal renal function	0.002	−0.011, 0.015	0.014	.712
Final step of analysis				
No. of previous contrast material administrations	0.010	0.011, 0.009	0.695	<.001
Analysis for globus pallidus–to-thalamus ratio				
First step of analysis				
Sex	0.001	−0.011, 0.013	0.006	.911
Age	0.000	0.000, 0.001	0.008	.874
No. of previous contrast material administrations	0.004	0.002, 0.006	0.285	<.001
Brain radiation therapy	−0.012	−0.025, 0.002	−0.125	.084
Tumor anywhere in body	−0.003	−0.017, 0.011	−0.025	.686
Brain tumor	−0.010	−0.029, 0.008	−0.082	.264
Chemotherapy	−0.008	−0.027, 0.011	−0.069	.398
Platinum-based chemotherapy	0.014	−0.004, 0.032	0.117	.125
Molecularly targeted therapy	0.019	−0.002, 0.039	0.107	.076
Abnormal liver function	0.021	−0.001, 0.042	0.096	.056
Abnormal renal function	0.007	−0.011, 0.024	0.037	.463
Final step of analysis				
No. of previous contrast material administrations	0.004	0.002, 0.006	0.288	<.001
Brain radiation therapy	−0.014	−0.025, −0.004	−0.151	.009
Liver abnormality	0.023	0.002, 0.044	0.107	.031

Note.—The R^2 for the dentate nucleus–to-pons signal intensity ratio was 0.491 for the first step of analysis and 0.483 for the final step of analysis; the R^2 for the globus pallidus–to-thalamus signal intensity ratio was 0.092 for the first step of analysis and 0.075 for the final step of analysis.

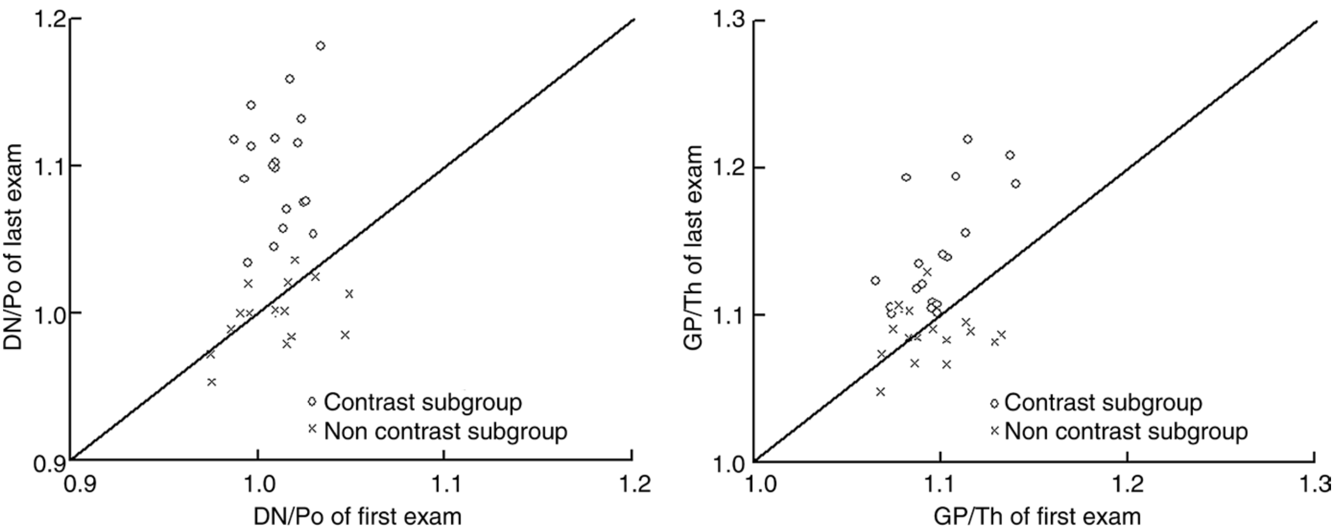
undergo numerous contrast-enhanced brain MR examinations. The T1 hyperintensity of the dentate nucleus seen in patients with multiple sclerosis may have more to do with the large cumulative gadolinium dose than the disease itself.

The mechanisms by which gadolinium administration causes high signal intensity in the dentate nucleus and globus pallidus on T1-weighted images remain unclear. Because the Gd^{3+} ion is quite toxic to mammals, it is usually synthesized as a complex with polyaminocarboxylic acid chelating agents. The chelated compound is generally well tolerated in humans, and these contrast agents have been regarded as highly stable pharmaceuticals (14,15). However, White et al (16) analyzed bone specimens from total hip arthroplasties 3–8 days after gadolinium-based contrast material administration by using inductively coupled plasma mass spectroscopy and reported Gd^{3+} deposition in the femora of patients with normal renal function who had received gadolinium-based contrast material. Animal studies have shown prolonged tissue retention of the administered gadolinium (17). The high signal intensity of the dentate nucleus and globus pallidus on unenhanced T1-weighted images may be due to gadolinium deposition in the brain independent of renal function, and the deposition may remain in the brain for a long time.

Our study has several limitations. Our hospital tends to transfer patients with end-stage disease to other hospitals and autopsy is seldom performed, making pathologic correlation with imaging findings impossible. In addition, we could not check all the imaging histories in other hospitals for each patient before admission to our institution. Thus, the number of exposures to gadolinium-based contrast material may have been underestimated. We found no correlation between renal function and globus pallidus or dentate nucleus signal intensities, which might have been a consequence of patients with impaired renal function tending not to undergo contrast-enhanced studies. The administered dose of gadolinium-based contrast material was not calculated according to patient weight, and so we could not measure the gadolinium-based contrast material doses as millimolars per kilogram. Our study was retrospective, and, despite the large number of patients available for cross-sectional analysis, the sample size of control subjects in the subgroups was small. Finally, because the signal intensity change is very small after a single administration of gadolinium-based contrast material, it could not be quantified after a single dose.

In conclusion, increased signal intensity in the dentate nucleus and, to a lesser extent, the globus pallidus

Figure 3



a. b.

Figure 3: **(a)** Scatterplot of dentate nucleus–to-pons ratio (*DN/Po*) at first study versus last study in contrast-enhanced and unenhanced examination subgroups. Solid line represents hypothetical line indicating that dentate nucleus–to-pons signal intensity ratio of first examination was equal to that of last examination. **(b)** Scatterplot of globus pallidus–to-thalamus ratio (*GP/Th*) at first study versus that at last study in contrast-enhanced and unenhanced examination subgroups. Solid line represents hypothetical line indicating that globus pallidus–to-thalamus signal intensity ratio of first examination was equal to that of last examination. Plots of contrast-enhanced examination subgroup are above the line, and dentate nucleus–to-pons and globus pallidus–to-thalamus ratios are seen to be increasing. Plots of unenhanced examination subgroup are near the line, showing that the change in dentate nucleus–to-pons and globus pallidus–to-thalamus ratios is small.

Table 3

Estimated Fixed Effect of Random Coefficient Model

Parameter	Estimated Value	Standard Error	*P* Value
Dentate nucleus–to-pons ratio			
β_0	0.9243	0.0117	<.001
β_1 (time)	0.0874	0.0093	<.001
β_2 (subgroup)	0.0871	0.0173	<.001
β_3 (time × subgroup)	−0.0896	0.0137	<.001
Globus pallidus–to-thalamus ratio			
β_0	1.0537	0.0085	<.001
β_1 (time)	0.0433	0.0066	<.001
β_2 (subgroup)	0.0488	0.0127	<.001
β_3 (time × subgroup)	−0.0514	0.0097	<.001

on unenhanced T1-weighted images showed positive correlation with previous exposure to gadolinium-based contrast material. Gadolinium deposition, or high-signal-intensity material deposition related to cumulative gadolinium load, occurs in the human brain independent of renal function. To elucidate the exact mechanism of the T1 hyperintensities in these areas, further evaluation on the basis of autopsy specimens and/or animal experiments will be needed.

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