Tepecik Eğit. ve Araşt. Hast. Dergisi 2021;31(2):195-202
doi:10.5222/terh.2021.60490

Signal Intensity Changes in the Dentate Nucleus and Globus Pallidus of Multiple Sclerosis Patients Undergoing Multiple Brain Magnetic Resonance Imaging with Gadolinium-Based Contrast Agents

Özgün Araştırma
Research Article

Gadolinyum Bazlı Kontrast Maddelerle Çoklu Beyin Manyetik Rezonans Görüntülemesi Yapılan Multipl Skleroz Hastalarının Dentat Çekirdek ve Globus Pallidustaki Sinyal Intensite Değişiklikleri

Yasin Ertuğ Çekdemir, Nuri Karabay

ABSTRACT

Objective: *To investigate the correlation between cumulative doses of gadolinium-based contrast agents and increased signal intensity (SI) in the dentate nucleus (DN) and globus pallidus (GP).*
Methods: *Our retrospective trial involved 21 multiple sclerosis patients (11 women, 10 men; mean age: 39.21±10.24, range: 20 to 57 years) who underwent a serial number of multiple cranial magnetic resonance imaging (MRI) examinations in the radiology department of our tertiary care center. Average signal intensities on the DN, pons, GP and thalamus on unenhanced T1-weighted magnetic resonance images were taken into account. The signal intensity in the DN was proportioned to the signal intensity in the pons, whereas the signal intensity in GP to the signal intensity in the thalamus. Any relationship between the DN-to-pons or GP-to-thalamus signal intensity ratios and previous gadolinium-based contrast administrations was sought by means of repeated measures ANOVA.*
Results: *Increases in both DN-to-pons and GP-to-thalamus signal intensity ratios displayed a significant correlation with previous administrations of gadolinium-based contrast agents (p<0.001 for both). A remarkable increase was detected in DN-to-pons and GP-to-thalamus signal intensity ratios between the first and last MRI examinations (p<0.001 for both).*
Conclusion: *Our results support the association between increase in the SI of the DN and GP to the number of gadolinium-enhanced MRI scans in MS patients. The increase in T1 SI seems to be linked with the number of enhanced MRI scans.*

Keywords: *Gadolinium; contrast media; dentate nucleus; globus pallidus; magnetic resonance imaging*

ÖZ

Amaç: *Gadolinyum bazlı kontrast maddelerin kümülatif dozları ile nükleus dentatus (DN) ve globus pallidustaki (GP) sinyal intensite(SI) artışı arasında ilişkiyi araştırmak*
Yöntem: *Çalışmamız üçüncü basamak hastanemizin radyoloji bölümünde retrospektif olarak gerçekleştirilmiş olup; çok sayıda kraniyal manyetik rezonans görüntülemesi (MRG) yapılmış olan multipl skleroz tanılı 21 olguyu (11 kadın, 10 erkek; ortalama yaş: 39.21 ± 10.24, dağılım: 20-57) içermekteydi. Kontrastsız T1 ağırlıklı MRG'de DN, pons, GP ve talamustaki ortalama sinyal intensite değerleri dikkate alındı. DN sinyal intensitesi, pons sinyal intensitesine, GP sinyal intensitesi ise talamus sinyal intensitesine oranlandı. DN-Pons ve GP-Talamus sinyal intensite oranları ile gadolinyum bazlı kontrast madde uygulamaları arasındaki ilişki, tekrarlı ölçümlerde ANOVA analizi ile saptandı.*
Bulgular: *Hem DN-Pons, hem de GP-Talamus sinyal intensite oranlarındaki artış, daha önceki gadolinyum bazlı kontrast madde uygulamalarıyla anlamlı bir korelasyon gösterdi (her ikisi için de p<0.001). Hastaların ilk ve son MRG incelemeleri arasında, DN-Pons ve GP-Talamus sinyal intensite oranlarında ise belirgin artış saptandı (her ikisi için p<0.001).*
Sonuç: *Bulgularımız, MS hastalarının DN ve GP'sindeki SI artışı ile gadolinyum bazlı kontrast maddelerle yapılan MRG incelemeleri arasındaki ilişkiyi desteklemektedir. T1 ağırlıklı görüntülerdeki SI artışı, kontrastlı MRG incelemelerinin sayısı ile bağlantılı görünmektedir.*

Anahtar kelimeler: *Gadolinyum, kontrast madde, nükleus dentatus, globus pallidus, bazal gangliyon, manyetik rezonans görüntüleme*

Received/Geliş: 04.05.2020
Accepted/Kabul: 13.08.2020
Published Online: 18.08.2021

Yasin Ertuğ Çekdemir
Dokuz Eylül Üniversitesi
Tıp Fakültesi,
Radyoloji Anabilim Dalı, Balçova
İzmir - Türkiye
dr_yasincekdemir@hotmail.com
ORCID: 0000-0002-3713-8826

N. Karabay 0000-0002-1059-5517
Dokuz Eylül Üniversitesi
Tıp Fakültesi,
Radyoloji Anabilim Dalı,
İzmir, Türkiye

Cite as: Çekdemir YE, Karabay N. Signal intensity changes in the dentate nucleus and globus pallidus of multiple sclerosis patients undergoing multiple brain Magnetic resonance imaging with gadolinium-based contrast agents. Tepecik Eğit. ve Araşt. Hast. Dergisi. 2021;31(2):195-202.

INTRODUCTION

Even if a single MRI test was performed, contrast enhancement can help determine the spread of lesions over time. The use of gadolinium-based contrast agents (GBCA) has long been advocated for MS patients [1,2].

In the diagnosis and therapy of patients with diverse neurological diseases, contrast-enhanced magnetic resonance imaging (MRI) plays a critical role. The majority of contrast-enhanced MRI exams employ one of several available contrast media, which are made up of a paramagnetic gadolinium (Gd) ion that has been chelated to reduce Gd3+ toxicity [3].

Gadolinium concentrations in various animal tissues after administration of different gadolinium-based contrast agents were found to differ significantly in preclinical studies [4,5]. A study found that hazardous components of gadolinium-based contrast agents (GBCA) such as ionic (gadopentate dimeglumine) and nonionic (gadodiamide) gadolinium-based contrast agents (GBCA) can persist in the body for a long time even in patients with normal renal function [6].

Within the human brain, gadolinium accumulates in the dentate nucleus (DN) and globus pallidus (GP). In individuals with neoplastic illness, hyperintensity in the DN and GP on unenhanced T1-weighted MR imaging was favorably linked with previous exposure to GBCA [6]. Patients who had contrast-enhanced MRI scan with GBCA had increased signal intensities (SI) on unenhanced T1-weighted images in the DN and GP regions of the brain [7-10].

Gadolinium accumulation in the brain has been reported in people with normal renal function in a prior investigation. The total number of contrast agent infusions and the signal intensity variations in the dentate nucleus on subsequent unenhanced T1-weighted images has been correlated significantly [2].

Multiple administrations of a GBCA resulted in increased SI in both the DN and the GP in patients with the relapsing-remitting subtype of multiple sclerosis (RRMS) [11]. Furthermore, Errante et al. claimed that SI on unenhanced T1-weighted images increased as the number of gadolinium-enhanced MRI exams in MS patients increased [12].

The objective of this study was to determine and quantify the relationship between the number of gadolinium-enhanced MRI exams and the SI of the DN and GP on unenhanced T1-weighted images in MS patients.

MATERIALS and METHODS

Study design

This retrospective trial was performed in the radiology department of a tertiary care center after the approval of the local Institutional Review Board (14.05.2015/2096GOA 2015/13-07) was obtained. All patients gave their written informed consent and adherence to the principles announced in Helsinki Declaration was ensured.

The data collected from medical records of 21 multiple sclerosis patients (11 women, 10 men) diagnosed based on modified McDonald criteria initially between October 2006 and June 2015 were analyzed [13]. All patients whose consecutive contrast-enhanced cranial MRI examinations (n≥4) were obtained at one-year intervals in the radiology department of our tertiary care center were included in the study.

Exclusion criteria were as follows: history of stroke, hemorrhage or ischemia of the brain, chemoradiotherapy, edema, tumor or other lesions in the cerebellum or the pons, intracranial infection such as meningitis or encephalitis, brainstem or cerebellar T2-hyperintense lesions, diagnosis of a brain tumor or brain metastases, hepatic or renal dysfunction, missing or unsatisfactory unenhanced T1-weighted MRI scans.

Since T1 hyperintensity in the GP has been associated with circumstances such as hepatic dysfunction, total parenteral nutrition, and hemodialysis, these patients were excluded from the study [2]. All patients had a normal renal function at the time of contrast administration (glomerular filtration rate > 60 mL/min/1.73 m^2).

Magnetic resonance imaging

All patients had their whole-brain imaging done on the same 1.5 T MRI scanner (Philips Achieva 1.5 T MRI, Philips Healthcare, Amsterdam, the Netherlands). Contrast-enhanced T1-weighted MR images were acquired after intravenous administration of a standard dose of 0.1 mmol/kg of body weight of the macrocyclic nonionic drug gadobutrol (Gadovist), linear nonionic gadolinium-based contrast agent gadodiamide (Omniscan), and gadoversetamide (OptiMARK) as described in the relevant literature [11].

The quantitative analysis was performed using software from Philips by two radiologists of expertise

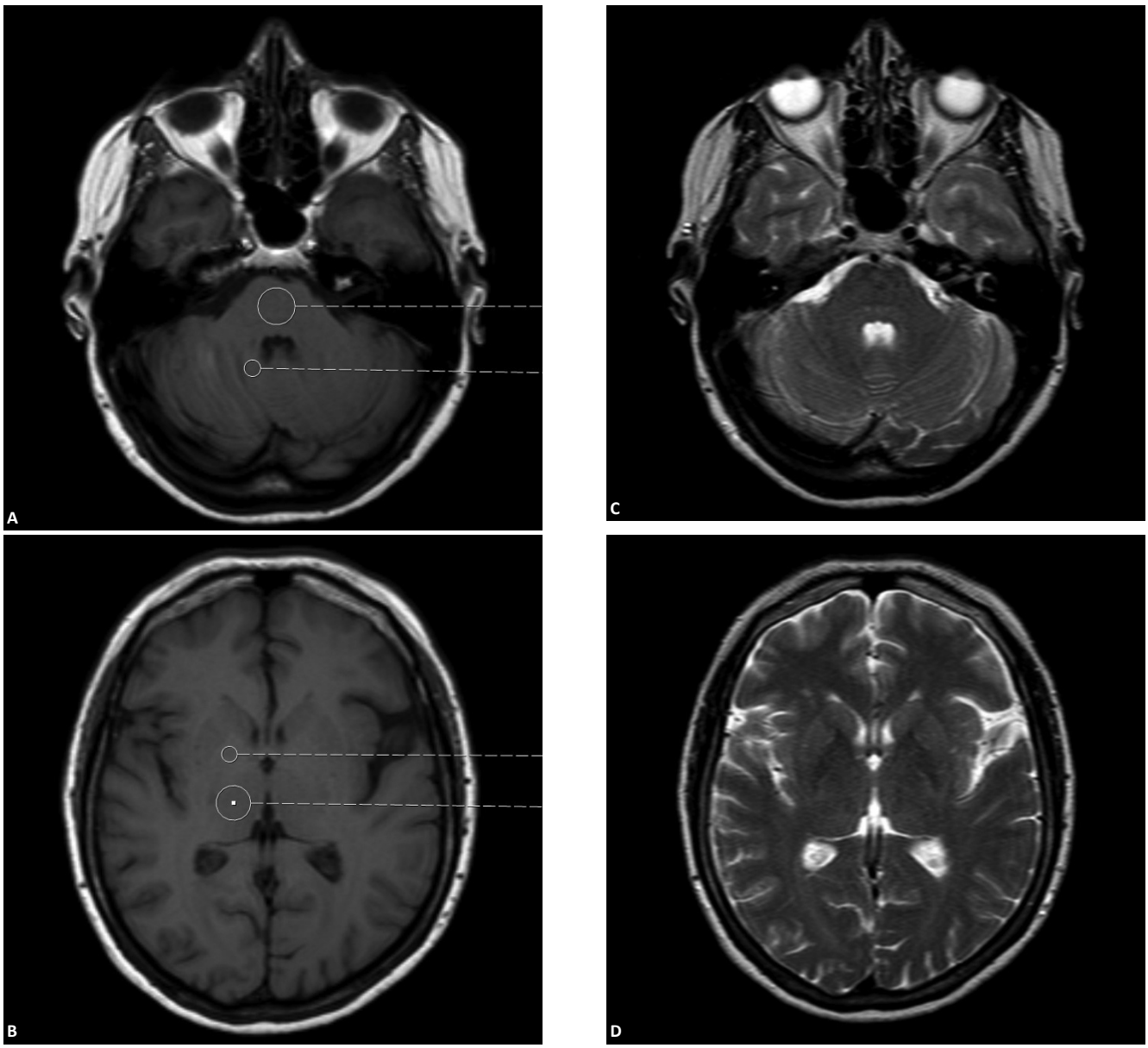

Figure 1a, b, c, d. Anatomic locations evaluated with axial T1-weighted images are verified with axial T2-weighted images.

in MS neuroimaging. These radiologists were unaware of the data and used unenhanced T1-weighted scans with operator-defined region-of-interest (ROI) assessments of mean SI, as described previously [5]. On the right side, oval ROIs were seen surrounding the central pons, as well as the DN, GP, and thalamus (Figure 1a-d). By consensus, the right ROI placement was determined, and all ROI measurements were completed in one session.

The proportion of ROI of 0.4 cm^2 at the level of right GP to the ROI of 1.2 cm^2 at right thalamus was taken into consideration. Similarly, the ratio of ROI of 0.4 cm2 at the level of the right dentate nucleus to the ROI of 1.2 cm^2 at pons was taken into consideration. The appropriate localization was confirmed via T2A views. Follow-up images were obtained from the same localizations. However, if lesions existed at these sites; measurements were made from the nearest normal tissue. No new lesions were detected at the sites where initial measurements were carried out.

Axial unenhanced T1-weighted spin echo images were obtained in accordance with the following parameters: section thickness, 5 mm; repetition time (msec)/ echo time (msec), 550/15; matrix size 256 x 256, and field-of-view (FOV): 240 mm.

For proton density and T2-weighted dual spin-echo (SE) sequences: section thickness, 5 mm; repetition time (msec)/ echo time (msec), 4000/20; matrix size 320x512, FOV: 230 mm and rectangular FOV: 85 mm.

T1 sequence with magnetization transfer (MT): section thickness, 5 mm; repetition time (msec)/ echo time (msec), 517/11; matrix size 280 x 256, FOV: 240 mm, and rectangular FOV: 85 mm.
Post-contrast T1 sequences: section thickness 5, mm; repetition time (msec)/ echo time (msec), 650/15; matrix size 256 x 256, FOV: 240 mm.

Statistical analysis

Analysis of data was performed via Statistical Package for Social Sciences (SPSS) software version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Differences between measurements were assessed with repeated measures ANOVA. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine whether the variables had a normal distribution. Since parametric conditions were met for the difference between repeated measurements, the comparison was made via ANOVA. Since there was a significant difference between these measurements, multiple comparative tests such as post-hoc pairwise comparisons and least significant difference (LSD) were performed. The significance level was defined at $p<0.05$.

RESULTS

Data were collected from files and MRI examinations of 21 MS patients (11 women, 53%; 10 men, 47%) with a mean age of 39.21±10.24 (range: 20 to 57) years. The average number of MRI examinations was 4.85 (range: 4 to 8).

The proportion of SI values measured in GP to the SI values in the thalamus (T) was taken into account on brain MRI examinations with contrast. Following the logarithmic transformation, all data was found to have a normal distribution. Repeated measures ANOVA indicated that F value was 98.96 and partial η2 was 0.832 ($p<0.001$) (Table 1). Significant differences were detected between the results of repeated measurements.

Table 1. Comparison of the average signal intensities in consecutive procedures as reflected in globus pallidus-to-thalamus (GP/T) and dentate nucleus-to-pons (DN/P) ratios.

GP/T measurement	Average ratio	Standard error	F	p-value
1st repetition	1.041	0.004	98.86	0.001*
2nd repetition	1.025	0.006		
3rd repetition	1.055	0.004		
4th repetition	1.041	0.004		
DN/P measurement	**Average ratio**	**Standard error**	**F**	**p-value**
1st repetition	1.025	0.006	56.45	0.001*
2nd repetition	1.041	0.004		
3rd repetition	1.054	0.005		
4th repetition	1.065	0.005		

*(Abbreviations: *: statistically significant; GP/T: globus pallidus-to-thalamus; DN/P: dentate nucleus-to-pons)*

The proportion of SI values in GP to SI values in the thalamus (T) was calculated and values in the first, second, third and fourth measurements were compared with each other (GP/T). The comparative differences between groups are shown in Table 2.

Table 2. Comparison of the average values of signal intensities for GP/T and DN/P ratios in various groups.

Groups compared for GP/T ratio	Difference between average values	Standard error	p-value
1-2	0.017	0.005	<0.001*
1-3	-0.014	0.003	<0.001*
1-4	0.001	0.005	<0.001*
2-3	-0.030	0.005	<0.001*
2-4	-0.016	0.003	<0.001*
3-4	0.014	0.004	<0.001*
Groups compared for DN/P ratio	**Difference between average values**	**Standard error**	**p-value**
1-2	-0.016	0.003	<0.001*
1-3	-0.030	0.004	<0.001*
1-4	-0.040	0.005	<0.001*
2-3	-0.014	0.002	<0.001*
2-4	-0.024	0.003	<0.001*
3-4	-0.010	0.001	<0.001*

*(Abbreviations: *: statistically significant; GP/T: globus pallidus-to-thalamus; DN/P: dentate nucleus-to-pons)*

The proportion of SI values measured in the dentate nucleus (DN) to the SI values in the pons (P) was evaluated (DN/P). All DN/P values were found to display normal distribution and repeated measures ANOVA demonstrated an F value of 56.45 and a partial η2 of 0.738 ($p<0.001$) (Table 1). There was a significant difference between ratios obtained in consecutive measures. The source of these differences was investigated by means of post hoc test (Table 2). Results of the analysis revealed that there were statistically significant differences between all groups ($p<0.001$).

DISCUSSION

The results of the current study support the presence of a link between hyperintensity of the DN and GP on unenhanced T1-weighted images and history of at least 4 gadolinium-enhanced MRI scans of MS patients.

Kasahara et al. demonstrated hyperintensity of the dentate nucleus on T1-weighted images of patients with neoplastic, degenerative, inflammatory, and demyelinating diseases [14]. They proposed that hyperintensity was more remarkable with the increasing dose of radiotherapy. We have excluded patients with a history of radiotherapy to eliminate the impacts of irradiation on alterations of the SI. Nevertheless, the total number of enhanced MRI scans was not considered in the clinical variables. It must be remembered that MS patients, especially those with a growing burden of lesions, may be associated with a history of serial gadolinium-enhanced brain MRI examinations.

Currently, two GBCAs without remarkable deposition in central nervous system are being used in our institution and our country. These agents consist of gadoterate meglumine (Dotarem) and gadobutrol (Gadovist).

Multiple doses of GBCA, particularly gadodiamide, were linked to increased SI of the dentate nucleus on unenhanced T1-weighted imaging in MS patients [12]. To limit the confounding influence of these variables on the SI changes of the GP and DN, we excluded individuals with kidney and/or liver disease in our investigation. Our findings support the hypothesis that gadolinium accumulates in the tissues of people with normal hepatic and renal function. Adin et al. suggested that T1 FLAIR sequences were less likely to reflect hyperintensity, whereas intensity differences were more remarkable in spin- echo sequences [15].

In a study, the hyperintensity of dentate nucleus/pons was found to be progressively increased in correlation with the number of contrasted -MRI examinations [12]. These series involved patients undergoing ≥6 MRI examinations; however, we noted a similar association with ≥4 MRI examinations. Moreover, the authors postulated that alterations in the SI of MS patients could not be attributed to the secondary progressive subtype of the disease. Shortening of T1 relaxation time in the dentate nucleus could be either linked with the direct impact

of accumulation of gadolinium or indirect effects of cellular changes due to gadolinium exposure [12]. A postmortem study was designed to compare neural tissues of 13 patients receiving GBCA medium with 10 patients in whom contrast medium was not used [16]. A noteworthy amount of gadolinium was detected in the DN, GP, thalamus and pons of patients that underwent MRI examination with gadolinium. Furthermore, increase in SI was correlated with the gadolinium dose administered [16].

The effect of T1 hyperintensity on DN and GP neuronal survival and function is unknown. More research is needed to determine the link between this radiological finding with motor or cognitive clinical functions. Because clinical data is scarce in the daily situation, radiologists should know how many enhanced MRI scans the patient has had previously. Multicenter prospective studies should be developed in this light. These experiments could also be used to assess the effects of various gadolinium-based contrast agents on the DN and GP's T1 SI [12].

Since free gadolinium is quite toxic, it should be bound to a ligand to be used as a contrast agent. Therefore, one of the mechanisms linked to the potential toxic effects of GBCAs is the release of gadolinium ions from the complex and deposition in tissues. This release is dependent on the stability of the GBCA in the biological environment, physicochemical features and the chemical structure of the complex. Therefore, commercially available gadolinium complexes are grouped into linear and macrocyclic subtypes [8].

Due to the toxicity of free gadolinium, it must be linked to a ligand before being utilized as a contrast agent. As a result, the release of gadolinium ions from the complex and their accumulation in tissues is one of the mechanisms connected to the potential harmful consequences of GBCAs. The stability of the GBCA in the biological milieu, as well as its physicochemical properties and chemical structure, are all factors that influence its release. As a result, gadolinium complexes on the market are divided into linear and macrocyclic subtypes [9].

Gibby et al. have shown that gadodiamide (linear, nonionic) was 2.5 times more likely to be deposited in bone tissue compared to gadoteridole (macrocyclic, nonionic) [16]. Various GBCA brands that are available for clinical use currently possess different chelating ligand molecules for the gadolinium chelate. The macrocyclic gadolinium chelates are substantially more resistant to dechelation than the nonionic linear gadolinium chelates. Gadolinium released and retained is lowest in macrocyclic GBCA, while it is greater for ionic linear GBCA and is greatest in the nonionic linear form of GBCA [17].

In relevant literature, data are limited to the findings derived from patients who display significant intracranial T1 shortening [6,7,12]. As suggested by Gibby et al [16], insoluble forms of gadolinium may constitute a significant percentage of all residual gadolinium in humans after the administration of GBCA in use today. It must be noted that insoluble GdPO4 may not have a known effectiveness at T1 shortening. Thus, it is possible that MRI may underestimate the amount of gadolinium retained in human tissues where it is detected and MRI alone may not be a reliable marker for determination of gadolinium [17].

Schlemm et al. proposed that the clinical implications of GBCA accumulation in brain are uncertain. Notably, they reported that T1 hyperintensity in DN of MS patients was related with gadopentate, but not gadobutrol administration. This finding yielded an explanation for the link between T1 hyperintensity with disease and its severity [18].

Therefore, there is clear evidence that administration of various GBCAs leads to accumulation of various amounts of gadolinium in the brain in the presence of normal hepatic and renal function. The clinical significance remains obscure and long-term impacts need to be investigated in further trials. Not only biodistribution and pharmacokinetics of GBCAs must

be studied in detail; but also, indications for contrast material-enhanced MRI examination must be carefully revisited.

The main limitations of the present study include small sample size, its cross-sectional design and lack of a control group. Our measurements have been made via 1.5 T and comparative trials with 3T are required to unveil the differences in terms of SI changes in GP and DN on T1-weighted images. Since the performance of MRI views in MS patients may not strictly adhere to a certain schedule, the relationship between time and SI changes could not be thoroughly elucidated. On the other hand, it must be remembered that having larger series of MS patients who undergo MRI with GBCA over a long period may be challenging for many tertiary care centers.

CONCLUSION

In conclusion, our results support the association between high SI of the DN and GP to the number of gadolinium-enhanced MRI scans in MS patients. The increase in T1 SI seems to be linked with the number of enhanced MRI scans. It must be kept in mind that GBCA may possess unknown risks and unnecessary use of contrast agents should be omitted. Administration of GBCA must be performed if potential benefits outweigh the risks and there is an effective route to excrete or eliminate the agent from the body. The amount, route and type of agent to be administered need to be determined on an evidence-based algorithms. Postmortem studies are particularly important to identify any deleterious effects of these substances. Further controlled, multicentric trials on larger series of MS patients with longer follow-up periods are warranted to authenticate our findings.

Acknowledgements
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Committee Approval: The approval of Dokuz Eylul University Non-Interventional Research Ethics Committee was obtained (2015/13-07).
Conflict of Interest: The authors declare no competing interest.
Funding: No financial support was received for this paper.
Informed Consent: Receipt.

REFERENCES

1. Traboulsee A, Simon JH, Stone L, Fisher E, Jones DE, Malhotra A, et al. Revised Recommendations of the Consortium of MS Centers Task Force for a Standardized MRI Protocol and Clinical Guidelines for the Diagnosis and Follow-Up of Multiple Sclerosis. AJNR Am J Neuroradiol. 2016;37:394-401. [CrossRef]
2. Malhotra A, LeSar B, Wu X, Durand D, Das N, Anzai Y, et al. Progressive T1 shortening of the dentate nucleus in patients with multiple sclerosis: result of multiple administrations of linear gadolinium contrast agents versus intrinsic disease. AJR Am J Roentgenol. 2018;211:1099-105. [CrossRef]
3. Giesel F, Mehndiratta A, Essig M. High-relaxivity contrast-enhanced magnetic resonance neuroimaging: a review. Eur Radiol. 2010;20:2461-74. [CrossRef]
4. Sieber MA, Pietsch H, Walter J, Haider W, Frenzel T, Weinmann HJ. A preclinical study to investigate the development of Nephrogenic Systemic Fibrosis: a possible role for gadolinium-based contrast media. Investig Radiol. 2008;43:65-75. [CrossRef]
5. Sieber MA, Lengsfeld P, Frenzel T, Golfier S, Schmitt-Willich H, Siegmund F, et al. Preclinical investigation to compare different gadolinium-based contrast agents regarding their propensity to release gadolinium in-vivo and to trigger nephrogenic systemic fibrosis-like lesions. Eur Radiol. 2008;18:2164-73. [CrossRef]
6. Kanda T, Ishii K, Kawaguchi K, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weightedMR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. Radiology 2014;270:834-41. [CrossRef]
7. McDonald RJ, McDonald JS, Kallmes DF, Jentoft ME, Paolini MA, Murray DL, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology 2015;275:772-82. [CrossRef]
8. Quattrocchi CC, Mallio CA, Errante Y, Cirimele V, Carideo L, Ax A, et al. Gadodiamide and dentate nucleus T1 hyperintensity in patients with meningioma evaluated by multiple follow-up contrast-enhanced magnetic resonance examinations with no systemic interval therapy. Invest Radiol. 2015;50:470-2. [CrossRef]
9. Radbruch A, Weberling LD, Kieslich PJ, Eidel O, Burth S, Kickingereder P, et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. Radiology 2015;275:783-91. [CrossRef]
10. Kanda T, Osawa M, Oba H, Toyoda K, Kotoku J, Haruyama T, et al. High signal intensity in dentate nucleus on unenhanced T1-weighted MR images: association with linear versus macrocyclic gadolinium chelate administration. Radiology

2015;275:803-9. [CrossRef]
11. Stojanov DA, Aracki-Trenkic A, Vojinovic S, Benedeto-Stojanov D, Ljubisavljevic S. Increasing signal intensity within the dentate nucleus and globus pallidus on unenhanced T1W magnetic resonance images in patients with relapsing-remitting multiple sclerosis: correlation with cumulative dose of a macrocyclic gadolinium-based contrast agent, gadobutrol. Eur Radiol 2016;26:807-15. [CrossRef]
12. Errante Y, Cirimele V, Mallio CA, Di Lazzaro V, Zobel BB, Quattrocchi CC. Progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance images is associated with cumulative doses of intravenously administered gadodiamide in patients with normal renal function, suggesting dechelation. Invest Radiol. 2014;49:685-90. [CrossRef]
13. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302. [CrossRef]
14. Kasahara S, Miki Y, Kanagaki M, Yamamoto A, Mori N, Sawada T, et al. Hyperintense dentate nucleus on unenhanced T1-weighted MR images is associated with a history of brain irradiation. Radiology 2011;258:222-8. [CrossRef]
15. Adin ME, Kleinberg L, Vaidya D, Zan E, Mirbagheri S, Yousem DM (2015) Hyperintense dentate nuclei on T1-weighted MRI: relation to repeat gadolinium administration. Am J Neuroradiol. 2015;36:1859-65. [CrossRef]
16. Gibby WA, Gibby KA, Gibby WA. Comparison of Gd DTPA-BMA (Omniscan) versus Gd HP-DO3A (ProHance) retention in human bone tissue by inductively coupled plasma atomic emission spectroscopy. Invest Radiol. 2004;39:138-42. [CrossRef]
17. Kanal E, Tweedle MF. Residual or retained gadolinium: practical implications for radiologists and our patients. Radiology 2015;275:630-4. [CrossRef]
18. Schlemm L, Chien C, Bellmann-Strobl J, Dörr J, Wuerfel J, Brandt AU, et al.Gadopentetate but not gadobutrol accumulates in the dentate nucleus of multiple sclerosis patients. Mult Scler 2017;23:963-72. [CrossRef]