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Increased signal intensity in the unenhanced T1-weighted magnetic resonance in the brain after repeated administrations of a macrocyclic-ionic gadolinium-based contrast agent

Makrosiklik-iyonik gadolinyum-bazlı kontrast ajan ile tekrarlanan uygulamalar ile T1 ağırlıklı kontrastsız manyetik rezonans görüntülemedeki sinyal intensite artışı

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Abstract

Aim: Gadoterate meglumine is a macrocyclic-ionic gadolinium-based contrast agent (GBCA) which is using in the magnetic resonance imaging (MRI). This study aims to determine the relationship between the signal intensity (SI) increase in the dentate nucleus (DN), pons (P), globus pallidus (GP), thalamus (T) and use gadoterate meglumine by repeated brain MRI in lung cancer patients.

Methods: The study was designed as a retrospective cohort study. The mean SIs of the DN, P, GP, and T and the cerebrospinal fluid (CSF) were measured in the unenhanced T1-weighted (T1w) images of the first and last MRIs of patients who underwent at least three brain MRI examinations with gadoterate meglumine. DN, P, GP, T SIs were divided by values obtained from CSF to standardize the SI measurements. The DN, P, GP, T SIs and DN/CSF, P/CSF, GP/CSF, T/CSF ratios were compared the first and the last MRI examinations.

Results: Our study revealed significant increases in DN, P, GP, and T SIs (P<0.001, P<0.001, P<0.001 and P=0.024, respectively). DN/CSF, P/CSF, GP/CSF, and T/CSF ratios were also significantly increased (P<0.001, P<0.001, P<0.001 and P=0.022, respectively). The number of examinations had a moderately strong positive correlation with in the DN/CSF ratio and a strong positive correlation with in P/CSF ratio (P<0.001 and P<0.001, respectively). There was a weak positive correlation between MRI intervals and in P/CSF ratio (P=0.037).

Conclusion: Our study suggested an increase in the first and the last MRI in DN, P, GP and T SIs related to the number and intervals of repeated examinations of a brain MRI with gadoterate meglumine among patients with lung cancer.

Keywords: Gadoterate meglumine, Brain, Magnetic resonance imaging, Signal intensity

Öz

Amaç: Manyetik rezonans görüntülemede (MRG) kullanılan makrosiklik-iyonik gadolinium- bazlı kontrast (GBKA) ajandır. Bu çalışmanın amacı gadoterat meglumin ile tekrarlıyan beyin MRG yapılmış akciğer kanserli hastalardaki dentat nucleus (DN), pons (P), globus pallidus (GP), talamusdaki (T) sinyal intensite (Sİ) artımı ile ilişkisini belirlemektir.

Yöntemler: Çalışma retrospektif kohort çalışması olarak tasarlanmıştır. Gadoterat meglumin ile en az üç ve daha fazla beyin MRG incelemesi yapılmış hastaların ilk ve son kontrastsız T1 ağırlıklı MRG incelemelerindeki DN, P, GP, T ve beyin omurilik sıvısındaki (BOS) ortalama Sİ'leri ölçüldü. DN, P, GP, T Sİ değerleri, Sİ ölçümlerini standartlaştırmak için BOS'dan elde edilen değerlere bölündü. DN, P, GP, T Sİ'leri ve DN/BOS, P/BOS, GP/BOS, T/BOS oranları ilk ve son MRG incelemelerinde karşılaştırıldı.

Bulgular: Çalışmamızda DN, P, GP ve T' Sİ'lerinde anlamlı şekilde artış saptandı (sırası ile P<0,001, P<0,001, P<0,001 ve P=0,024). DN/BOS, P/BOS, GP/BOS, T/BOS oranlarının anlamlı şekilde arttığı tespit edildi (sırası ile P<0,001, P<0,001, P<0,001 ve P=0,022). Çekim sayısının; DN/BOS oranı ile arasında orta düzeyde; P/BOS oranı ile arasında yüksek düzeyde pozitif yönlü korelasyon saptandı (sırası ile P<0,001 ve P<0,001). MRG çekim aralıkları ve P/BOS oranı ile arasında hafif düzeyde pozitif yönlü korelasyon mevcuttu (P=0,037).

Sonuç: Çalışmamızda akciğer kanserli hastalarda gadoterat meglumin ile tekrarlayan beyin MRG çekimlerinde, çekim sayısı ve aralıkları ile ilişkili olarak DN, P, GP ve T Sİ'lerinde ilk ve son MRG'ler arasında bir artış olduğu gösterilmiştir.

Anahtar kelimeler: Gadoterat meglumin, Beyin, Manyetik rezonans inceleme, Sinyal intensite

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Introduction

Gadolinium-based contrast agents (GBCAs) are extensively used to enhance contrast in magnetic resonance imaging (MRI). GBCAs enhance the tissue contrast by virtue of their shortening effect of the T1 relaxation time of the living tissues. Gadolinium (Gd) is a rare- earth heavy metal which is highly toxic to humans in its free form and is used as bound by ligands when used as a contrast agent. It is bound to chelating agents to form linear forms (gadodiamide, gadopentetate dimeglumine and gadoxetate disodium) and macrocyclic (gadoteridol, gadobutrol and gadoterate meglumine). While macrocyclic molecules, form a completely enclosed cage enveloping the Gd ion, linear molecules form partial cages wrapped around the Gd ion and are not completely closed [1,2]. Furthermore, GBCAs are subgrouped as ionic and non-ionic based on their charge. As the electrostatic interaction of ionic GBCAs with chelates is more intense, they are considered more stable than non-ionic agents [1].

In the recent few years, many studies reporting a concentration-dependent deposition of Gd in the brain, characterized by high signal intensities (SI) on unenhanced T1-weighted (T1w) images, have been published. Previous studies showed that Gd mostly accumulates in globus pallidus (GB) and dentate nucleus (DN) [1,2]. There is a well-documented association between T1w image hyperintensities in the GP and DN and multiple administrations of linear GBCAs [3-7]. On the other hand, macrocyclic GBCAs are known to not accumulate in the brain and are therefore considered to be extremely safe. However, the latest studies in the literature have contradicted previous knowledge regarding the safety of the macrocyclic GBCAs. It has been shown that administration of gadobutrol, a macrocyclic-non-ionic GBCA, is also associated with T1w SI changes in the brain [8,9]. Moreover, Rossi Espagnet et al. [10] reported that macrocyclic-ionic GBCA gadoterate meglumine caused an increase in the brain T1w SI in a pediatric population.

However, there is a paucity of studies specifically addressing a possible association between T1 hyperintensities in the brain and multiple administrations of gadoterate meglumine in the adult population.

The aim of the current study was to investigate the relation between the SI increase in the DN, P, GP, T and the use gadoterate meglumine by repeated brain magnetic resonance imaging (MRI) in lung cancer patients.

Materials and methods

Patient population

The ethical compliance of this study was approved in accordance with the Helsinki Declaration by the Hospital Local Ethics Committee, Ankara, Turkey. The medical records of a total of 758 patients who were diagnosed with lung cancer and followed exclusively at the medical oncology service of our hospital between September 2015 and January 2019 were retrospectively assessed. Among patients who underwent at least three MRI examinations after intravenous gadoterate meglumine administration, those that met the inclusion criteria were enrolled. Inclusion criteria were as follows: (a) unenhanced T1w images were obtained before the first GBCA administration; (b) all of the consecutive MR imaging examinations were performed exclusively at our institution in the same MRI scanners. The exclusion criteria were as follows: (a) being examined at another hospital using GBCAs; (b) patients who were found to have undergone contrast-enhanced MRI examinations with contrast material containing intravenous or intraarticular gadolinium; (c) patients with a brain mass; (d) patients with brain metastasis; (e) patients with Alzheimer's disease; (f) history treatment of radiation; (g) history of the metabolic disease: (h) history of metal toxicity; (ı) history of multiple sclerosis; (j) history of total parenteral nutrition containing manganese; (k) history of nephrogenic systemic fibrosis; (l) history of brain stroke, or history of brain ischemia; (m) patients with laboratory findings consistent with renal or liver failure in simultaneous biochemical studies with the latest MRI examination; (n) patients with artifacts precluding a proper MRI examination.

A total of 61 patients (mean 57.85 years; age range, 18–69 years) with available data on the first and the last examinations with unenhanced T1-weighted images were included.

Imaging acquisition

All MRI were performed using two 1.5T MRI scanners (Magnetom, Aera, Siemens, Erlangen, Germany) and Philips Achieva (Philips Medical Systems, Eindhoven, The Netherlands) with a standard head coil.

The brain MR protocol included axial T1w, axial T2-weighted imaging, sagittal fluid-attenuated inversion recovery imaging, and axial, sagittal, coronal contrast-enhanced T1w. The axial unenhanced T1-weighted spin-echo images were obtained using the following parameters: repetition time (TR)/echo time (TE): 348/8.9 ms, voxel size: 0.7x0.7x0.5 mm, the field of view (FOV): 23x23 cm, slice thickness: 5 mm. All patients' measurements were performed over the axial unenhanced T1w spin-echo sequence.

Gadoterate meglumine is the only GBCA used at our institution for all contrast-enhanced MRI studies. Contrast-enhanced T1w images were obtained after intravenous injection of a standard dose of 0.1 mmol/kg of body weight of gadoterate meglumine (Dotarem®, Guerbet, Istanbul, Turkey).

Image analysis and measurements

MRI evaluations were performed on a picture archiving and communication system (Extreme PACS, Ankara, Turkey). Quantitative analysis was conducted by two radiologists (R.P.K. and M.Ö. with 10 and 7 years of experience, respectively), who were blinded to the serial number of the MRI scan. By consensus, they used the unenhanced T1w images of each patient (mean, 5 mm; range, 4–7 mm) circular region-of-interest (ROI) measurements of mean SI as previously described [3]. All of the ROI measurements were manually drawn.

SIs were quantified from the neuroanatomic regions of DN in pink and pons (P) in blue (Figure 1 a), ROIs were drawn at the left DN, P in the first (Figure 1 b) and the last unenhanced T1w images (Figure 1 c). SIs were quantified from the neuroanatomic regions of GP in red and thalamus (T) in green (Figure 2 a), ROIs were drawn at the left GB and T in the first (Figure 2 b) and the last unenhanced T1w images (Figure 2 c).

SIs were quantified from the neuroanatomic region of the cerebrospinal fluid (CSF) at the fourth ventricle level in

yellow (Figure 3 a), ROIs were drawn at the CSF in the first (Figure 3 b) and the last unenhanced T1w images (Figure 3c). Axial T2-weighted images were used as guidelines to confirm the correct placement of the ROIs.

DN, P, GP, T mean SIs were divided by mean values obtained from CSF to standardize the SI measurements as previously described [11]. The DN, P, GP, T SIs and DN/CSF, P/CSF, GP/CSF, T/CSF ratios were compared the first and the last MRI examinations.

Statistical analysis

The smallest significant difference that can be accepted between the positive and negative groups of the test in the T1 sequence of DN, one of the regions to be examined, was calculated as 26 [6], at least 23 cases for 5% Type I error and 90% power.

Statistical analysis was performed using SPSS Version 24 (SPSS Inc., Armonk, NY, USA). The data were analyzed using Kolmogorov–Smirnov, and Skewness–Kurtosis tests for normal distribution. The temporal change of the data was compared with the paired t-test. Categorical variables were compared with quantitative data using the Mann-Whitney U test; quantitative data were compared with one another using the Spearman correlation test. Mean and standard deviation values were used for analysis. *P*-values less than 0.05 were considered statistically significant.

Results

Demographic and characteristics of study population

The study population had a mean age of 57.85 years; 67.2% were women. The mean frequency of MRI examinations was 3.31 (0.46), with at least three and at most five MRIs having been taken. The mean interval between two MRI examinations was 26.28 (4.81) months, with the shortest interval being 16 months and the longest 34 months.

MRI Results

There were a significant increase in the SIs of DN, DN/CSF ratio, P, P/CSF ratio, GP, GP/CSF ratio, T and T/CSF ratio ($P<0.001$, $P<0.001$, $P<0.001$, $P<0.001$, $P<0.001$, $P<0.001$, $P=0.024$ and $P=0.022$, respectively). The largest SI difference was between DN and GP; when proportioned to CSF, the largest difference was found in DN/CSF ratio and P/CSF ratio (Table 1).

The differences in DN/CSF, P/CSF, GP/CSF, and T/CSF ratios were similar in men and women ($P=0.440$, $P=0.396$, $P=0.054$ and $P=0.099$, respectively) (Table 2).

No correlation was found between age and differences ratios of DN/CSF, P/CSF, GP/CSF, T/CSF ($P=0.675$, $P=0.955$, $P=0.142$ and $P=0.607$, respectively).

The number of examinations had a moderately positive correlation with the DN/CSF ratio and a strongly positive correlation with the P/CSF ratio ($P<0.001$ and $P<0.001$, respectively). No correlation was found between the ratios in GP/CSF and T/CSF and examination frequency ($P=0.506$ and $P=0.051$, respectively). There was a weakly positive correlation between MRI examination intervals and P/CSF ratio ($P=0.037$). No correlation was found between MRI examination intervals and ratios in DN/CSF, GP/CSF, and T/CSF ($P=0.902$, $P=0.215$ and $P=0.164$, respectively) (Table 3).

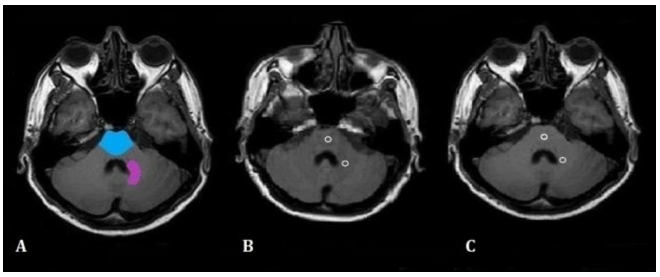

Figure 1: Axial unenhanced T1-weighted images demonstrating the anatomical locations of nucleus dentatus in pink and pons in blue (A), and the exact locations of the region of interest (ROI) where the measurements were performed at the left dentate nucleus and pons in the first (B) and the last MRI (C) examinations of the patient

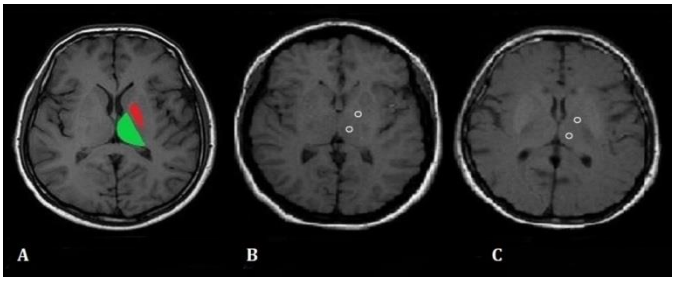

Figure 2: Axial unenhanced T1-weighted images demonstrating the anatomical locations of globus pallidus in red, and thalamus in green (A), and the exact locations of the region of interest (ROI) where the measurements were performed at left globus pallidus and left thalamus in the first (B) and the last MRI (C) examinations of the patient

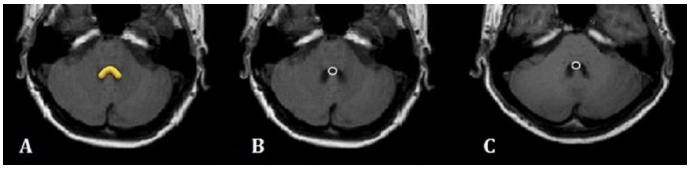

Figure 3: Axial unenhanced T1-weighted images demonstrating the anatomical locations of the fourth ventricle in yellow (A), and the exact locations of the region of interest (ROI) where the measurements were performed in the first (B) and the last MRI (C) examinations of the patient

Table 1: SIs and ratios differences in the first and last MRI examinations

	First MRI examination Mean (SD)	Last MRI examination Mean (SD)	Difference Mean (SD)	*P*-value *
DN	269.26 (3.16)	283.33 (12.95)	14.07 (13.51)	<0.001*
DN/CSF	3.45 (0.29)	4.25 (0.24)	0.8 (0.37)	<0.001*
P	277.02 (3.4)	280.84 (1.62)	3.82 (4.29)	<0.001*
P/CSF	3.28 (0.44)	4.17 (0.25)	0.88 (0.51)	<0.001*
GP	227.95 (2.25)	232.51 (1.41)	4.56 (2.64)	<0.001*
GP/CSF	2.51 (0.28)	3.22 (0.18)	0.7 (0.31)	<0.001*
T	262.79 (1.38)	263.44 (1.68)	0.66 (2.21)	0.024*
T/CSF	3.63 (0.29)	3.76 (0.32)	0.13 (0.43)	0.022*

* Paired t-test, P values less than 0.05 were considered statistically significant, SD: Standart deviation, MRI: Magnetic resonance imaging, DN: Nucleus dentatus, P: Pons, T: Thalamus, GB: Globus pallidus, CSF: Cerebrospinal fluid

Table 2: The ratios differences according to the gender

	Gender		*P*-value *
	Female (n=41) Mean (SD)	Male (n=20) Mean (SD)	
DN/CSF	0.78 (0.39)	0.84 (0.31)	0.440*
P/CSF	4.29 (4.02)	2.85 (4.76)	0.396*
GP/CSF	0.64 (0.32)	0.85 (0.26)	0.054*
T/CSF	0.20 (0.42)	0.02 (0.42)	0.099*

* Mann-Whitney U, SD: Standard deviation, P values less than 0.05 were considered statistically significant, DN: Nucleus dentatus, P: Pons, T: Thalamus, GB: Globus pallidus, CSF: Cerebrospinal fluid

Table 3: Correlation of age, number of MRI and time interval in the ratios

	Age		Number of MRI		Time interval	
	r	*P*-value	r	*P*-value	r	*P*-value *
DN/CSF	0.055	0.675*	0.490	<0.001*	-0.016	0.902*
P/CSF	-0.007	0.955*	0.577	<0.001*	0.268	0.037*
GP/CSF	-0.190	0.142*	0.087	0.506*	-0.161	0.215*
T/CSF	0.067	0.607*	0.251	0.051*	0.181	0.164*

* Spearman correlation, r: Correlation coefficient, P values less than 0.05 were considered statistically significant, MRI: Magnetic resonance imaging, DN: Nucleus dentatus, P: Pons, T: Thalamus, GB: Globus pallidus, CSF: Cerebrospinal fluid

Discussion

More than 30 million examinations are performed with GBCAs and more than 300 million doses are used each year worldwide [12,13]. Until Marckmann et al. [14] reported that some GBCAs could cause nephrogenic systemic fibrosis (NSF) in patients with renal failure in 2006, GBCAs have been

extremely popular in that they were safe. NSF is a potentially morbid and fatal systemic disorder with skin and internal organ involvement, which is characterized by progressive extensive fibrous tissue accumulation following GBCAs use in patients with acute or chronic renal failure [15]. Fortunately, no new cases of NSF have been reported after the renal glomerular filtration rate assessment prior to GBCAs administration became a routine application. Thus, the perception of safety regarding GBCAs continued. However, in 2014, Kanda et al. [3] pointed out that GBCAs might be the cause of increased SI of DN and GB on unenhanced T1-weighted images of patients with normal renal function undergoing contrast-enhanced MRI. These increases correlated with the number of contrast-enhanced MRI examinations. Subsequent autopsy studies showing the accumulation of Gd in many tissues, including brain have prompted a review of the safety of GBCAs [16-18]. It is still unclear why, to what extent, and in which organs does Gd accumulate and how important is this accumulation [19]. Although brain Gd accumulation is considered not to cause asymptomatic clinical presentation, the heavy-metal family (manganese, iron, and copper) to which Gd belongs has been implicated in the development of parkinsonism by accumulating in the brain [19,20].

Although it has been formerly shown that linear GBCAs accumulate in brain tissue and cause the appearance of hyperintensity in T1w unenhanced examinations, there are still various views for the accumulation of macrocyclic GBCAs in the brain [1]. Radbruch et al. [11] compared the groups that underwent multiple examinations with linear-ionic GBCA (gadopentetate dimeglumine) and gadoterate meglumine and reported that gadopentetate dimeglumine caused an SI increase owing to its accumulation in DN and GP. Robert et al. [21], in an experimental study on rats, compared subjects administered repeated linear-nonionic (gadodiamide) and gadoterate meglumine to show that the group that received gadodiamide had hyperintensity in DN while there was no change in the group that received gadoterate meglumine. Ryu et al. compared linear-ionic GBCA (gadopentetate dimeglumine) and gadoterate meglumine in a pediatric population and showed that gadopentetate dimeglumine caused hyperintensity in DN and GP whereas gadoterate meglumine did not [22]. In a study on rats, Lohrke et al. [23] reported some 15-time higher brain tissue concentration of linear GBCAs compared to macrocyclic GBCAs and reported that Gd's chelating stability played an important role in this observation. Lee et al. [24], on the other hand, reported no intensity increase in DNs and GPs of patients that undergone at least 2 MRI examinations with macrocyclic-ionic GBCA. Renz et al. [25] compared linear-ionic GBCA (gadopentetate dimeglumine) and macrocyclic-nonionic GBCA (gadobutrol) among pediatric patients who underwent more than three examinations with GBCA; they reported hyperintensity in both GP and DN in both groups. They stressed that macrocyclic GBCAs caused hyperintensity as much as linear GBCAs. Stojanov et al. [8] detected hyperintensity in DN, GP, and P following multiple macrocyclic-nonionic GBCA (gadobutrol) use in patients with multiple sclerosis. Rossi Espagnet et al. [10] in a study on pediatric patients, revealed that gadoterate meglumine led to hyperintensity at the level of GP, DN, and P. Kartamihardja et al. [26] in an animal experiment, showed that Gd deposits forming in macrocyclic-ionic GBCA administered subjects were excreted from the brain over time whereas the deposits remained in substantial quantities in those who were administered linear-nonionic GBCAs. In an autopsy study, Murata et al. described Gd accumulation in the brains of patients administered linear GBCAs and macrocyclic GBCAs, with the most substantial accumulation having been in GP and DN [18]. We detected the highest SI suggesting brain gadolinium accumulation in DN and GP among patients that underwent multiple MRI with gadoterate meglumine. The difference between linear GBCAs and macrocyclic GBCAs reported in the literature may basically stem from macrocyclic GBCAs accumulating in the brain to a very small extent. Such studies show variations with respect to age, race, and selected patient groups. It should be remembered that the GBCAs doses are administered by patient weight and weight-adjusted contrast material doses play a significant role. Furthermore, there is no standardization of measurement parameters between those studies. Compared to CSF, the largest difference ratios were found for DN/CSF and P/CSF; although we considered that this difference may have been due to blood flow coming to those regions and, hence, agent's excretion, more studies are needed in this subject.

McDonald et al. [27] reported that the cumulative Gd dose showed a strong correlation with tissue Gd concentration in basal ganglia and posterior fossa as well as changes in T1w SI following at least four GBCA administrations. Radbruch et al. [11] reported that SI increased in DN and GP in T1w images originated from administering serial linear-ionic GBCA and was correlated to the number of examinations. Errante et al. [28] showed a relationship in the form of regression between the number of MRI examinations taken with linear-nonionic GBCA (gadodiamide) and increased SI. We detected a positive correlation between the number of examinations and in DN/CSF ratio and P/CSF ratio but not with the ratios in GP/CSF and T/CSF. We believe that tissue contrast builds up to increase SI values with each examination over time.

Jost et al. [29], in a rat study, reported that SI increases in DN and P by 24 hours after GBCAs administration. Stojanov et al. [8] found out that a greater rate of hyperintensity as the interval between the examinations shortened among patients with multiple sclerosis who were administered macrocyclic-nonionic GBCA (gadobutrol). Frentzel et al. [30] reported that Gd dissociated from linear chelates after a 15-day period; linear Gds' dissociation rate was greater than that of macrocyclic forms; macrocyclic chelates were more stable than linear ones. We detected a correlation between MRI examination interval and in P/CSF ratio but not with ratios in DN/CSF, GP/CSF, and T/CSF. This may be due to excretion of GBCA from different parts of the brain over time due to its half-life. Furthermore, it may be related to time to being excreted from tissues with GBCA stabilities.

The retrospective nature of the study created some limitations. All measurements were done manually over the images obtained by the 1.5-T MRI device by standard brain protocol sections. Acquisition of thin, continuous sections with a 3T MRI device may enable obtaining images with better

resolution, providing more precise results. GBCA doses are adjusted by patients' body weight. As we did not know the patients' body weights, we had no information about the total dose of the Gd.

Conclusion

In conclusion, our study shows the increase in SI in the DN, GP, P, and T due to the use of gadoterate meglumine in unenhanced T1w images. Although its clinical effects remain unknown, for the time being, one should be aware of Gd accumulation. We are of the opinion that doctors should be cautious about the use of macrocyclic-ionic GBCA, gadoterate meglumine, which is considered safe. This subject should be further studied by multicenter standardized trials.

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