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# Gadolinium Deposition in Brain after Intravenous Injection of Gadolinium-based Contrast Agents

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**Abstract**

***Background:*** *Gadolinium-based contrast agents (GBCA) are commonly used in MRI. GBCA have been linked to signal changes in dentate nucleus and globus pallidus.*

***Purpose:*** *To assess the degree of gadolinium accumulation in brain structures among patients with GBCA administrations.*

***Materials and methods:*** *Retrospective study included 224 patients: 197 patients who underwent more than two MRI with linear-type GBCA and 27 patients from control group who underwent at least two MRI without GBCA.*

***Results:*** *Statistical analysis of the main group revealed positive correlation between difference in signal intensity of GP/thalamus ratio to the number of previous MRI with GBCA (r=0.145, p=0.042), with a time interval between first and last MRI (r=0,221, p=0,002), as well as to patients age (r=0.145, p=0.042). For difference in ND/ pons ratio positive correlation was found only with the number of previous studies with GBCA (r=0.172, p=0.016).*

*Statistical analysis of patients who received GBCA of the same type (gadodiamide or gadopentetic acid) revealed the following correlations: in patients who were administered gadodiamide, a positive correlation was found between ND/pons ratio and the number of previous studies with GBCA (r=0,280, p<0,5). In patients who were administered gadopentetic acid, no correlation was found between the difference in GP/thalamus ratio, in ND/pons ratio and the number of studies with GBCA.*

***Conclusions:*** *Increased signal intensity at the pale globes and the dentate nuclei on pre-contrast images may be related to the number of studies performed with linear-type GBCA.*

**Key-words:** Gadolinium Deposition, Gadolinium-containing Linear-type Contrast Media, Gadodiamide, Gadopentetic Acid, Magnetic Resonance Imaging.

**Key Results.** Increased signal intensity at the pale globes and the dentate nuclei on pre-contrast images may be related to the number of studies performed with linear-type GBCA. Among the patients who were administered gadopentetic acid, no correlation was found between the number of studies (MRI scans) and SI increase at ROI.

**Summary Statement.** The proposed model of SI dependence on time may correspond to the possible gadolinium washout effect.

## 1. Introduction

Gadolinium-based contrast agents (GBCA) are widely used in clinical practice for contrast enhanced MRI (CE-MRI). First they were employed in 1988[1]; since then, numerous studies have looked into the potential of GBCA in diagnosing various body systems. The current value of this method is far beyond original expectations, and is one of the most important tools for diagnosis worldwide.

GBCA on are tolerated well by patients when used in accordance with the instructions; however, like any other agents used in clinical practice, they have potential risks and adverse effects. According to various sources, mild allergic reactions occur with a frequency of 0.004-0.7%; life-threatening anaphylactic shock is observed in range of 0.001-0.01% [2].

Gadolinium safety is a highly debated issue. Toxicity of gadolinium ions is leveled by their binding to chelate complexes.

Differences in GBCA structure are reflected in difference in physicochemical properties. GBCA can be divided into two groups: linear or open type and macrocyclic type in which Gd3+ ion is enclosed in a ligand ring. Different types of contrast agents have different stability, i.e. ability to hold toxic Gd3+ ion within the complex. Despite the fact that linear-type GBCA cause more significant changes in signal intensity (SI) at basal nuclei (due to lower thermodynamic and kinetic stability) than substances of macrocyclic type, gadolinium deposition is observed in both occasions [3] [4].

In 2006, studies conducted by Grobner demonstrated a correlation between GBCA administration and nephrogenic systemic fibrosis in patients with renal dysfunction [5], [6]. In 2014, Kanda revealed a correlation between gadolinium administrations and high SI on T1 at the dentate nuclei (ND) and the pale globes (GP) regardless of renal function [19]. This consistent pattern was revealed by other authors [7] - [18]. All these studies drew attention to GBCA safety; however,

possible effects of gadolinium deposition on humans are still unknown [2]. It was also found that gadolinium deposition at ND, pons, GP and thalamus occurs irrespective of pathological changes in the brain which could lead to the disruption of blood-brain barrier integrity. In 2016, a study assessed the parkinsonism rate among patients who underwent MRI with and without GBCA: the authors found no significant difference in these groups [21]. Taking into account the rationale of the issue, the purpose of the research is to assess the presence and the degree of gadolinium deposition in brain among patients with multiple injections of GBCA, to identify any differences in the degree of gadolinium accumulation depending on the type of contrast agent, and to assess the dynamics of SI changes as an indirect feature of the possible washout effect.

## 2. Materials and Methods

The study included 224 patients. The first group consisted of patients (197) who underwent 2-16 scans (3.6 on average) with GBCA (gadodiamide or gadopentetic acid, 0.2 ml/kg body weight). The average age was 47.9 years (5–81), 74 males and 123 females. The second group included 27 patients who underwent 2-3 scans (2.1 on average) without GBCA. The average age was 23.8 years (10-45), 14 males and 13 females. All the MRI of the second group (without GBCA) were performed due to epilepsy. In group 1, 52 patients were administered gadodiamide, 59 patients were administered gadopentetic acid, the rest (86) were administered various GBCA.

### Inclusion Criteria

patients without GBCA administration;

patients who underwent more than two MRI scans with GBCA (gadodiamide or gadopentetic acid);

patients who had undergone more than two MRI scans without GBCA;

normal renal function (GFR> 60 ml/min);

normal liver function (reference range of blood biochemical analysis);

MRI scans were performed on the same scanner using the same pulse sequences.

### Exclusion Criteria

Contraindications for GBCA.

Abnormal liver function.

Studies conducted with GBCA in the previous history.

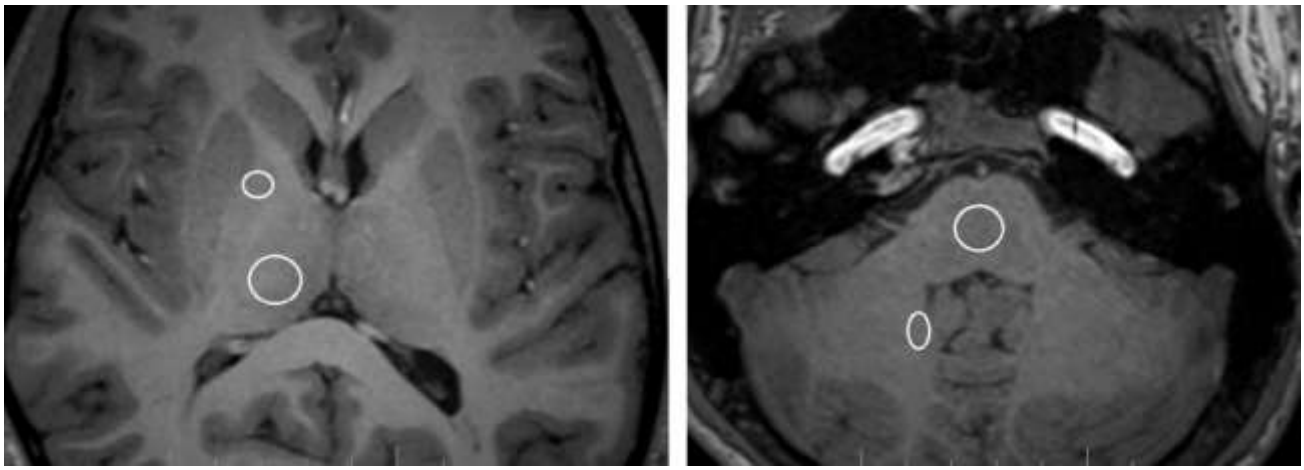
Gender and age, number of scans with GBCA, and the time interval between the first and the last scans were taken into account.

All the MRI imaging was performed on Siemens Magnetom Verio 3T scanner. All the patients underwent the same pulse sequence: pre-contrast T1 in sagittal plane and subsequent reformation in in the axial and the frontal planes. Pre-contrast T1 were obtained using following parameters: TR – 1780, TE – 2.78, slice – 0.8 mm, matrix – 320x320, FOV – 256x256mm. The parameters were identical in all the patients. The measurements were carried out on reformations in the axial plane, 0.8mm slice.

Quantitative analysis (SI assessment) was carried out independently by two radiologists (with 4 and 20 years of work experience).

The study is based on retrospective SI assessment on T1 in GP and ND on the right of control areas by highlighting the corresponding regions of interest (ROI) (Fig.1). The control areas are the right thalamus (T) and the central parts of pons (P). If SI measurement on the right was not possible (due to a tumor, edema, cystic transformation, etc.), the measurement was conducted on the corresponding ROI on the left. The SI ratio was assessed by dividing the SI value of ND by the SI from central parts of pons, by dividing the SI from GP by the SI from the central parts of thalamus in the first (1) and the last (2) scans. Estimating the SI ratio correlations of the corresponding points (GP2/T2 – GP1/T1, ND2/P2 – ND1/P1) is the purpose of the statistical analysis.

Figure 1- An Example of Measuring the Intensity of the MR Signal on Pre-contrast Images. On the right, Measurements are Carried out in the Region of the Pale Globe and the Thalamus, On the Left, in the Region of the Dentate Nucleus and the Central Parts of the Pons



Statistical analysis was performed using the statistical software package STATISTICA 10 (USA) to identify correlations between the ratio of ND/pons and GP/thalamus and following factors: gender, age, number of previous GBCA MRI scans, and the time interval between the first and the last GBCA MRI scan.

## 3. Results

The statistical analysis among the first group of patients revealed a positive correlation between the difference in the ratio of GP/thalamus with the number of MRI scans with GBCA (r=0.145, p=0.042), with a time interval between the first and the last MRI scans (r=0.221, p=0.002), as well as with the patients' age (r=0.145, p=0.042) (Fig.2). For the difference in ND/pons ratio, a positive correlation was only noted with the number of previous scans with GBCA (r=0.172, p=0.016) (Fig.3).

Figure 2- Distribution of differences in the GP/thalamus Ratio among Patients in Group 1 Depending on the Observation Time, the Number of Scans and Age

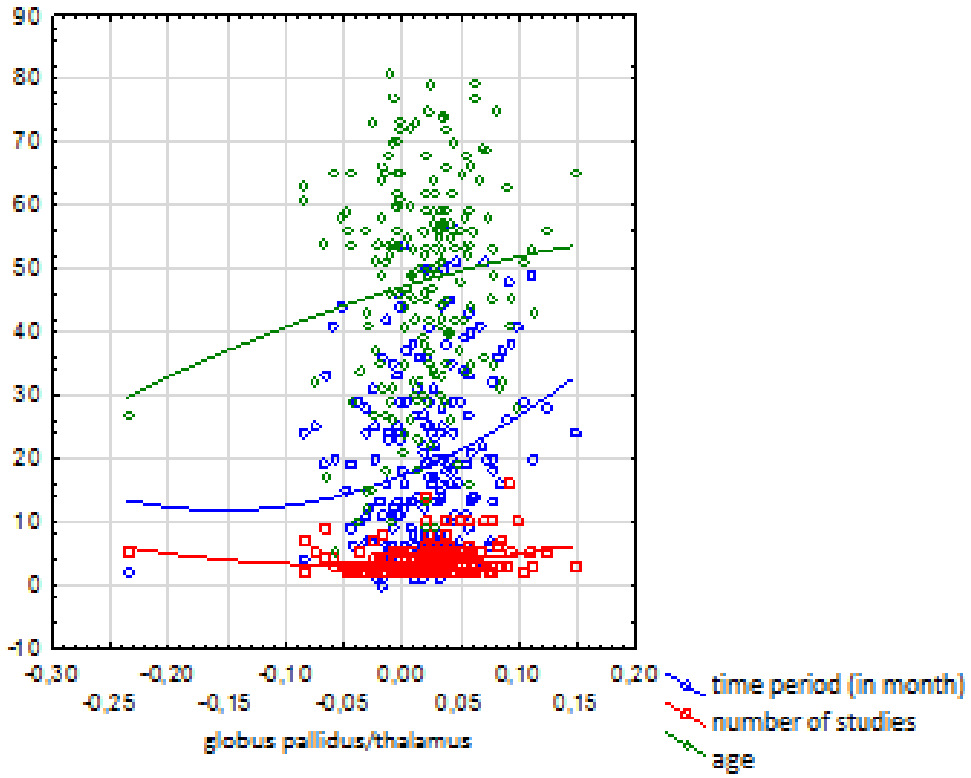




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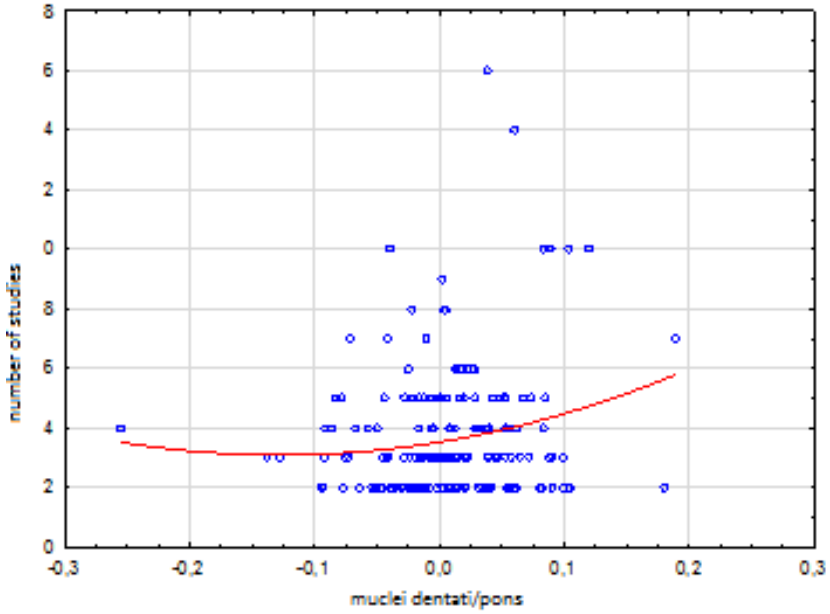
Figure 3- Distribution of differences in the ND/pons Ratio among Patients in Group 1 Depending on the Number of Scans




When dividing patients of Group 1 into 3 subgroups (Fig. 4) depending on age (under 39, 40-60, 61 and older), the following correlations were found (Table 1):

Figure 4 - Distribution of Patients in Group 1 into 3 Subgroups Depending on Age

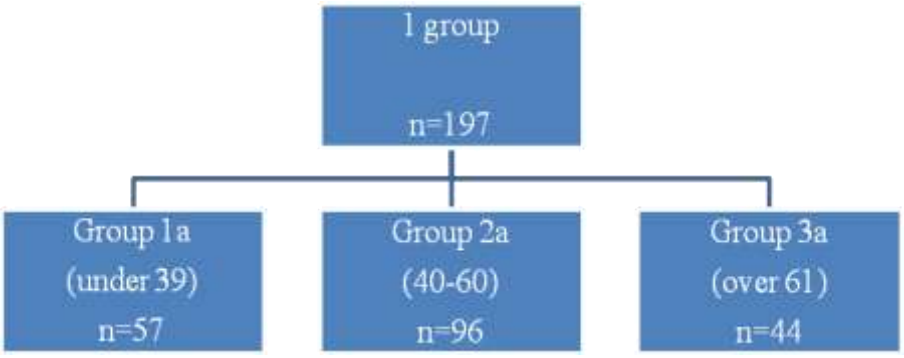



Table 1- Localization of SI changes depending on the observation period and the number of studies with GBCA among the patients of different age groups

| | Under 39 years | 40-60 years old | Over 61 years |
|---|---|---|---|
| Observation period | – | Globus pallidus (GP2/T2 – GP1/T1) | – |
| Number of MRI examination with IV contrasting | Nuclei dentati (ND2/P2-ND1/P1) | Globus pallidus (GP2/T2 – GP1/T1) | – |

- among the patients of Group 1a, no positive correlation between the difference in the GP/thalamus ratio and the dependencies of interest was revealed. A positive correlation

was revealed between the difference in ND/pons ratio and the number of scans (r=0.264, p=0.047).

- among the patients of Group 2a (40-60 years), a positive correlation was found between the difference in the GP/thalamus ratio and the number of scans (r=0.303, p=0.003) and the observation period (r=0.317, p=0.002). No positive correlation was found between ND/pons and the dependencies of interest.
- among the patients of Group 3a (61 and older), no significant correlations were found.

Among the patients of the second group (without GBCA), no significant correlation between the difference in SI ratios of corresponding ROI and the dependencies described above was found.

When comparing the ratios of SI indicators, the average values in the first and last studies with GBCA changed at the level of GP by 1.817%, and at the level of ND by 0.772%.

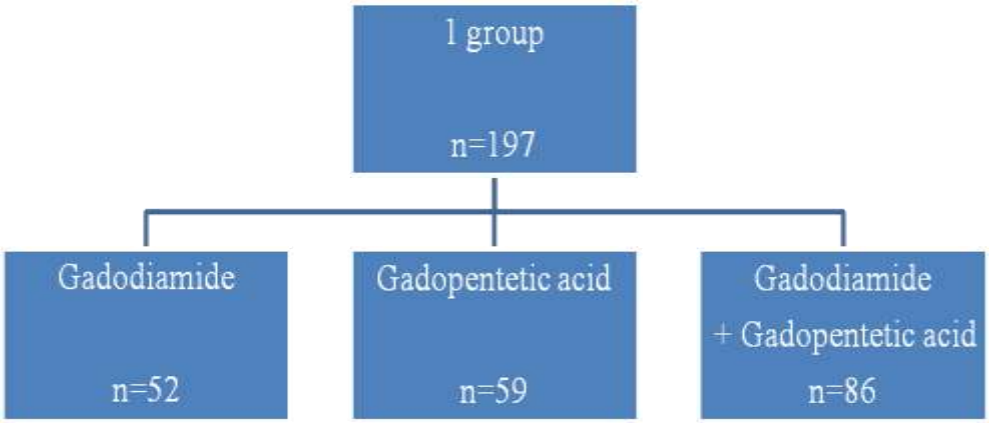
Average data for all the parameters are presented in Table 2.

Table 2- SI–signal Intensity on T1, GP–pale Globe, T–thalamus, ND–dentate Nucleus, P–pons, 1–values for First Study, 2–values for Last Study.
*Data are Presented as Average

| Parameters | 1 group (with GBCA) | 2 group (without GBCA) |
|---|---|---|
| Age* | 47,9 (5-81) | 23,8 (10-45) |
| Gender | men - 74 | men - 3 |
| | women - 123 | women - 4 |
| Number of studies (MRI scans)* | 3,6 (2-16) | 2,1 (2-3) |
| Observation period (months)* | 19,1 (0-57) | 10,1 (3-21) |
| SI1 pale globe* | 463,3 | 457,7 |
| SI1 thalamus* | 455,7 | 451,3 |
| SI1 dentate nucleus* | 456,1 | 465 |
| SI1 pons* | 464,1 | 474,5 |
| SI2 pale globe* | 465,9 | 454,2 |
| SI2 thalamus* | 450 | 454,5 |
| SI2 dentate nucleus* | 460,4 | 455,2 |
| SI2 pons* | 464,7 | 469,7 |
| GP1/T1* | 1,018 | 1,014 |
| GG2/T2* | 1,036 | 0,999 |
| ND1/P1* | 0,983 | 0,979 |
| ND2/P2* | 0,991 | 0,97 |
| GP2/T2-GP1/T1* | 0,018 | -0,015 |
| ND2/P2-ND1/P1* | 0,007 | -0,009 |

When dividing the patients of Group 1 depending on GBCA type (Fig.5), the following correlations were found: if gadodiamide was administered, a positive correlation was found between the ND/pons ratio and the number of previous studies with GBCA (r=0.280, p<0.5). If gadopentetic acid was administered, a positive correlation was found between the difference in the GP/thalamus ratio and age (r=0.324, p<0.5).

Figure 5- Distribution of Patients in Group 1 Depending on GBCA




To assess the SI dynamics, the authors of the present study used an ordinary differential equation $\frac{dI}{dt} = -kI$, where **I** is SI, and k is the coefficient of SI changes. The solution is $I(t) = I_0 e^{-kt}$, where $\mathbf{I_0}$ is the initial signal intensity (Fig.6). The values of the k coefficient for the studied structures are given in Table 3.

Figure 6 - SI decline Curve

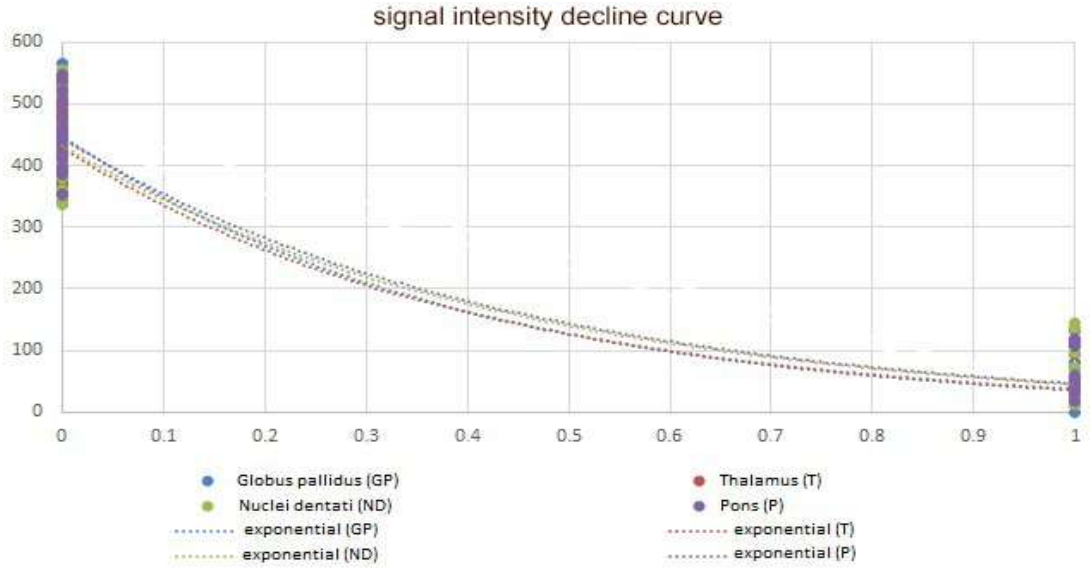


Table 3- *Mean Absolute Error (Average Absolute Error) - Model Quality Rating

| Locus | coefficient $k$ | MAE* |
|---|---|---|
| GP | 0.00668 | 48.0539 |
| Thalamus | 0.00711 | 51.1068 |
| ND | 0.00632 | 53.2144 |
| Pons | 0.00658 | 45.2909 |

## 4. Discussion

As already mentioned, GBCA safety is a highly debated issue. It was revealed that an increased SI at GP and ND is associated with the number of previous studies with linear-type GBCA. This consistent pattern can be traced in the present research; however, the correlation coefficient value is between 0.145-0.172, which indicates an extremely weak correlation. When comparing the SI ratios, the mean values in the first and the last studies with GBCA increased at the level of GP by 1.817%, and at the level of ND by 0.772%. If only gadodiamide was administered, a correlation was found between the number of previous studies with GBCA and the increased SI at the level of ND. If gadopentetic acid was administered, no correlation was found between the number of studies and the SI increase at ROI, which contradicts the published data; correlations are observed only with age. This is probably due to the small number of samples and a relatively small number of studies per patient as relating to the main group and the group of patients who were administered gadodiamide: 2-14 studies were conducted among patients with gadodiamide, 2-16 in the general group of patients, and 2-7 in the group with gadopentetic acid. Obviously, the absence of any correlations in the control group indicates the absence of gadolinium deposition; this may also be due to the small sample.

## 5. Conclusion

Possible effects of gadolinium deposition on the human body have not yet been established. It was shown that SI at T1 and T2 at basal nuclei among healthy volunteers positively correlate with age. This is due to the deposition of iron at the level of brain corresponding areas (primarily pale globes, red nuclei, reticular formation, to a lesser extent, dentate nuclei [22]. The present study revealed that signs of gadolinium deposition are only observed in 1a and 1b age groups (up to 39 and 40-60 years). In the third age group (over 61 years), the above described consistent pattern was not

observed. However, this may also be due to the accumulation of iron ions at the basal nuclei among older patients. The increased SI on T1 from GP is also observed with various toxic (CO2 poisoning, methanol poisoning), metabolic (liver disease accompanied by the accumulation of iron, copper or ammonium), degenerative (Gallewarden-Spatz disease) or neoplastic processes (neurofibromatosis I type) [23].

In several papers, gadolinium deposition at the basal nuclei was confirmed according to autopsy data. The presence or absence of iron ions or other metabolites was not evaluated. In one of these studies, gadolinium ions were found in the brain of patients without GBCA administration [7], [24]. The source of gadolinium in this case may be the environment, for instance, wastewater [25].

It should be taken into account that an increase in SI at the basal nuclei is also observed when using contrast agents of the macrocyclic type [24]; however, this consistent pattern is not traced in all the studies [26].

The model of SI dependence on time is of undoubted interest. Theoretically, this consistent pattern can speak in favor of gadolinium washout effect. The trend was first demonstrated in 2015 by Adin et al. [27]; later, this hypothesis was confirmed in experiments on rats [28].

These inconsistencies may indicate that earlier observation demonstrated no washout, while follow-ups revealed it. The authors of the present research believe this part to be most significant and promising on the subject.

## References


Lohrke, J., Frenzel, T., Endrikat, J., Alves, F.C., Grist, T.M., Law, M., & Pietsch, H. (2016). 25 years of contrast-enhanced MRI: developments, current challenges and future perspectives. *Advances in therapy*, *33*(1), 1-28.

Ramalho, M., Ramalho, J., Burke, L.M., & Semelka, R.C. (2017). Gadolinium retention and toxicity—an update. *Advances in chronic kidney disease*, *24*(3), 138-146.

Gulani, V., Calamante, F., Shellock, F.G., Kanal, E., & Reeder, S.B. (2017). Gadolinium deposition in the brain: summary of evidence and recommendations. *The Lancet Neurology*, *16*(7), 564-570.

McDonald, R.J., McDonald, J.S., Dai, D., Schroeder, D., Jentoft, M.E., Murray, D.L., & Kallmes, D.F. (2017). Comparison of gadolinium concentrations within multiple rat organs after intravenous administration of linear versus macrocyclic gadolinium chelates. *Radiology*, *285*(2), 536-545.

Grobner, T. (2006). Gadolinium–a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrology Dialysis Transplantation*, *21*(4), 1104-1108.

Marckmann, P., Skov, L., Rossen, K., Dupont, A., Damholt, M.B., Heaf, J.G., & Thomsen, H.S. (2006). Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *Journal of the American Society of Nephrology, 17*(9), 2359-2362.

Kanda, T., Fukusato, T., Matsuda, M., Toyoda, K., Oba, H., Kotoku, J.I., & Furui, S. (2015). Gadolinium-based contrast agent accumulates in the brain even in subjects without severe renal dysfunction: evaluation of autopsy brain specimens with inductively coupled plasma mass spectroscopy. *Radiology, 276*(1), 228-232.

Ramalho, J., Castillo, M., Al Obaidy, M., Nunes, R.H., Ramalho, M., Dale, B.M., & Semelka, R.C. (2015). High signal intensity in globus pallidus and dentate nucleus on unenhanced T1-weighted MR images: evaluation of two linear gadolinium-based contrast agents. *Radiology, 276*(3), 836-844.

Weberling, L.D., Kieslich, P.J., Kickingereder, P., Wick, W., Bendszus, M., Schlemmer, H.P., & Radbruch, A. (2015). Increased signal intensity in the dentate nucleus on unenhanced T1-weighted images after gadobenate dimeglumine administration. *Investigative radiology, 50*(11), 743-748.

Roberts, D.R., & Holden, K.R. (2016). Progressive increase of T1 signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images in the pediatric brain exposed to multiple doses of gadolinium contrast. *Brain and Development, 38*(3), 331-336.

Radbruch, A., Weberling, L.D., Kieslich, P.J., Hepp, J., Kickingereder, P., Wick, W., & Bendszus, M. (2015). High-signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted images: evaluation of the macrocyclic gadolinium-based contrast agent gadobutrol. *Investigative radiology, 50*(12), 805-810.

Cao, Y., Huang, D.Q., Shih, G., & Prince, M.R. (2016). Signal change in the dentate nucleus on T1-weighted MR images after multiple administrations of gadopentetate dimeglumine versus gadobutrol. *American Journal of Roentgenology, 206*(2), 414-419.

Kanda, T., Osawa, M., Oba, H., Toyoda, K., Kotoku, J.I., Haruyama, T., & Furui, S. (2015). High signal intensity in dentate nucleus on unenhanced T1-weighted MR images: association with linear versus macrocyclic gadolinium chelate administration. *Radiology, 275*(3), 803-809.

Quattrocchi, C.C., Mallio, C.A., Errante, Y., Cirimele, V., Carideo, L., Ax, A., & Zobel, B.B. (2015). 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. *Investigative radiology, 50*(7), 470-472.

Radbruch, A., Weberling, L.D., Kieslich, P.J., Eidel, O., Burth, S., Kickingereder, P., & Bendszus, M. (2015). Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. *Radiology, 275*(3), 783-791.

McDonald, R.J., McDonald, J.S., Kallmes, D.F., Jentoft, M.E., Murray, D.L., Thielen, K.R., & Eckel, L.J. (2015). Intracranial gadolinium deposition after contrast-enhanced MR imaging. *Radiology, 275*(3), 772-782.

Stojanov, D.A., Aracki-Trenkic, A., Vojinovic, S., Benedeto-Stojanov, D., & Ljubisavljevic, S. (2016). 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. *European radiology, 26*(3), 807-815.

Errante, Y., Cirimele, V., Mallio, C.A., Di Lazzaro, V., Zobel, B.B., & Quattrocchi, C.C. (2014). 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. *Investigative radiology, 49*(10), 685-690.

Kanda, T., Ishii, K., Kawaguchi, H., Kitajima, K., & Takenaka, D. (2014). 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. *Radiology, 270*(3), 834-841.

McDonald, R.J., Mc Donald, J.S., Kallmes, D.F., Jentoft, M.E., Paolini, M.A., Murray, D.L., & Eckel, L.J. (2017). Gadolinium deposition in human brain tissues after contrast-enhanced MR imaging in adult patients without intracranial abnormalities. *Radiology, 285*(2), 546-554.

Welk, B., Mc Arthur, E., Morrow, S.A., Mac Donald, P., Hayward, J., Leung, A., & Lum, A. (2016). Association between gadolinium contrast exposure and the risk of parkinsonism. *Jama, 316*(1), 96-98.

Aquino, D., Bizzi, A., Grisoli, M., Garavaglia, B., Bruzzone, M.G., Nardocci, N., & Chiapparini, L. (2009). Age-related iron deposition in the basal ganglia: quantitative analysis in healthy subjects. *Radiology, 252*(1), 165-172.

Hegde, A.N., Mohan, S., Lath, N., & Lim, C.T. (2011). Differential diagnosis for bilateral abnormalities of the basal ganglia and thalamus. *Radiographics, 31*(1), 5-30.

Kanda, T., Nakai, Y., Hagiwara, A., Oba, H., Toyoda, K., & Furui, S. (2017). Distribution and chemical forms of gadolinium in the brain: a review. *The British journal of radiology, 90*(1079), 20170115.

Hatje, V., Bruland, K.W., & Flegal, A.R. (2016). Increases in anthropogenic gadolinium anomalies and rare earth element concentrations in San Francisco Bay over a 20 year record. *Environmental science & technology, 50*(8), 4159-4168.

Lee, J.Y., Park, J.E., Kim, H.S., Kim, S.O., Oh, J.Y., Shim, W.H., & Kim, S.J. (2017). Up to 52 administrations of macrocyclic ionic MR contrast agent are not associated with intracranial gadolinium deposition: multifactorial analysis in 385 patients. *PloS one, 12*(8), e0183916.

Adin, M.E., Kleinberg, L., Vaidya, D., Zan, E., Mirbagheri, S., & Yousem, D.M. (2015). Hyperintense dentate nuclei on T1-weighted MRI: relation to repeat gadolinium administration. *American Journal of Neuroradiology, 36*(10), 1859-1865.

Smith, A.P., Marino, M., Roberts, J., Crowder, J.M., Castle, J., Lowery, L., & Evans, P.M. (2017). Clearance of gadolinium from the brain with no pathologic effect after repeated administration of gadodiamide in healthy rats: an analytical and histologic study. *Radiology, 282*(3), 743-751.

McDonald, R.J., McDonald, J.S., Kallmes, D.F., Jentoft, M.E., Murray, D.L., Thielen, K.R., & Eckel, L.J. (2015). Intracranial gadolinium deposition after contrast-enhanced MR imaging. *Radiology, 275*(3), 772-782.

Robert, P., Violas, X., Grand, S., Lehericy, S., Idée, J.M., Ballet, S., & Corot, C. (2016). Linear gadolinium-based contrast agents are associated with brain gadolinium retention in healthy rats. *Investigative radiology, 51*(2), 73-82.