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Gadolinium deposition in the brain of patients with relapsing-remitting multiple sclerosis after 10 years of follow-up

Taloženje gadolinijuma u mozgu bolesnika sa relapsno-remitentnom multiplom sklerozom nakon 10 godina praćenja

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Abstract

Background/Aim. Since 2014 and the publication of the results of the first study on the accumulation of gadolinium contrast, we have witnessed a growing body of evidence on the deposition and retention of gadolinium in the brain after the use of gadolinium-based contrast agents (GBCAs). However, there is still no strong clinical evidence of the adverse effects of GBCAs on the brain parenchyma. The aim of the study was to determine the existence of gadolinium deposits in the brain of patients with relapsing-remitting multiple sclerosis after a ten-year follow-up period. During this period, the patients have regularly, each year, undergone magnetic resonance imaging (MRI) with the administration of gadolinium contrast (gadopentetate dimeglumine – Magnevist®) in order to follow the course of the disease. **Methods.** A cohort of 20 patients was formed for the purpose of this study. The ratio of the values of the signal intensity (SI) of different regions of the brain-to-cerebrospinal fluid (CSF) was compared for each patient on the initial MRI examination and the MRI examination ten years later. **Results.** Frontal cortex-to-CSF ($p < 0.01$), occipital cortex-to-CSF ($p < 0.01$), the white matter of the *corona radiata*-to-CSF ($p < 0.01$), parietal cortex-to-CSF ($p < 0.05$), thalamus-to-CSF ($p = 0.051$), putamen-to-CSF ($p = 0.06$), and anterior and posterior limb of the *capsula interna*-to-CSF ($p = 0.062$) SI ratios increased after multiple gadopentetate administrations. An increase in the absolute values of the T1-weighted (T1W) signal in three-quarters of patients was registered in the frontal and occipital cortex and cerebellar hemispheres. A slightly smaller increase in SI, but still greater than 55–65%, was registered in structures of the parietal cortex, putamen, *cornu* anterior and posterior of the *capsula interna*, *corpus callosum* (CC) *splenium*, *pons*, thalamus, *nucleus caudatus*, *substantia nigra*, CC *genu*, and temporal cortex. **Conclusion.** In the cohort of 20 patients, there was a statistically significant increase in SI in the pre-contrast T1W sequence in the following structures: frontal, parietal, and occipital cortex, as well as supratentorial white matter. This result speaks in favor of the existence of chronic accumulation of gadolinium contrast agent gadopentetate dimeglumine in brain structures.

Key words:
gadolinium dtpa; long term adverse effects; magnetic resonance imaging; multiple sclerosis, relapsing-remitting.

Apstrakt

Uvod/Cilj. Od 2014. godine kao i od objavljivanja rezultata prve studije o akumulaciji kontrastnih sredstava na bazi gadolinijuma (*gadolinium-based contrast agents* – GBCAs), svedoci smo sve većeg broja dokaza o taloženju i zadržavanju gadolinijuma u mozgu nakon primene ovih sredstava. Međutim, još uvek nema jakih kliničkih dokaza o štetnim efektima GBCAs na moždani parenhim. Cilj rada bio je da se utvrdi postojanje naslaga gadolinijuma u mozgu kod bolesnika sa relapsno-remitentnom multiplom sklerozom nakon desetogodišnjeg perioda praćenja. Tokom ovog perioda, bolesnici su redovno, svake godine, bili podvrgnuti pregledu magnetnom rezonancom (MR) koji je uključivao davanje linearnog kontrastnog sredstva (gadopentetat dimeglumin – Magnevist®) kako bi se pratio tok bolesti. **Metode.** Za potrebe ove studije formirana je kohorta od 20 bolesnika. Za svakog bolesnika je upoređivan

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odnos vrednosti intenziteta signala (IS) u različitim regionima mozga i IS cerebrospinalnog likvora (CSL) na inicijalnom pregledu primenom MR i na pregledu deset godina kasnije primenom iste metode. **Rezultati.** Odnosi IS frontalnog korteksa i CSL-a ($p < 0,01$), okcipitalnog korteksa i CSL-a ($p < 0,01$), bele mase *corona radiata* i CSL-a ($p < 0,01$), parijetalnog korteksa i CSL-a ($p < 0,05$), talamusa i CSL-a ($p = 0,051$), putamena i CSL-a ($p = 0,06$) i *cornu anterior* i *posterior capsula interna* i CSL-a ($p = 0,062$) povećali su se nakon višestruke primene gadopentetata. Porast apsolutnih vrednosti *T1-weighted* (T1W) signala kod tri četvrtine bolesnika registrovan je u frontalnom i okcipitalnom korteksu i hemisferi malog mozga. Nešto manje povećanje IS, ali ipak veće od 55–65%, registrovano je u strukturama kao što su: parijetalni korteks, putamen, *cornu anterior* i *posterior capsula interna*, *corpus callosum* (CC) *splenium*, *pons*, talamus, *nucleus caudatus*, *substantia nigra*, CC *genu* i temporalni korteks. **Zaključak.** U kohorti od 20 bolesnika pokazano je statistički značajno povećanje IS u prekontrastnoj T1W sekvenci u sledećim strukturama: frontalnom, parijetalnom i okcipitalnom korteksu, kao i beloj masi *corona radiata*. Rezultati govore u prilog tome da postoji hronično deponovanje gadolinijumskog kontrastnog sredstva, gadopentetat dimeglumina, u moždanim strukturama.

Ključne reči:
gadolinijum dtpa; neželjeni efekti, dugoročni; magnetska rezonanca, snimanje; multipla skleroza, relapsno-remitentna.

Introduction

Since 1988, after being approved by the Food and Drug Administration (FDA), gadolinium-based contrast agents (GBCAs) have been widely used in magnetic resonance imaging (MRI) [1]. Today they are used in about 30% of MRI diagnostics [2].

They have long been considered safe to use, and in 2006, cases of potentially lethal nephrogenic systemic fibrosis (NSF) caused by the use of GBCAs were described in patients with renal insufficiency [3, 4].

After the initial report in 2014, gadolinium depositions in the brain have mainly been found in the *nucleus dentatus* (ND) and *globus pallidus* (GP), mostly associated with linear GBCAs [5, 6]. Many studies have indicated the occurrence of gadolinium uptake in the grey matter, thalamus, *pons*, and white matter [6, 7]. Since 2014, studies on gadolinium depositions in the brain have focused on detection, distribution, potential toxicity, and clinical consequences [8].

In addition to deposition in these regions, deposition in other regions of the brain but of lower intensity has also been proven. Furthermore, several studies have found that GBCAs can be deposited in other organs, including the skin, bones, and liver, despite normal renal function [9–11]. This study aimed to determine the existence of contrast deposition in different areas of the brain in patients with relapsing-remitting (RR) multiple sclerosis (MS).

Methods

Subject population

The study was conducted as a retrospective study of a series of observational cases. It included 20 patients with RR MS treated with a unique immunomodulatory protocol (interferon beta 1b) for ten years after the diagnosis of MS at the Clinic of Neurology of the Military Medical Academy (MMA), Belgrade, Serbia. The study protocol followed the Declaration of Helsinki and was approved by the Ethics Committee of the MMA on January 21, 2016. Informed consent was obtained from each patient.

Inclusion criteria were: both genders aged 24 to 51 years with RR MS (according to the revised McDonald criteria); neurologically determined functional disability (Extended Disability Status Scale – EDSS ≤ 6); clinically and/or radiologically active MS in the previous year (the review was performed for reasons other than MS). All patients signed informed consent.

Exclusion criteria were: other central nervous system diseases; head trauma; renal or hepatic insufficiency; psychiatric diseases; malignancy; use of psychoactive substances; pregnancy.

In 20 patients, 8 (40%) men and 12 (60%) women, with an average age of 38.9 ± 6.6 years and a mean disease duration of 5.8 ± 7.0 years, after neurological examination, at the Institute of Radiology of the MMA, Belgrade, Serbia, a standard MRI of the brain was performed with one initial and at least one follow-up examination *per* year over a 10-year follow-up period, which included the administration of a linear contrast agent (gadopentetate dimeglumine – Magnevist®), in the amount of 0.2 mL/kg of body weight (Table 1).

Table 1

Demographic characteristics of the patients

Parameter	Male	Female
Gender, n (%)	8 (40)	12 (60)
Age, mean ± SD	33.2 ± 6.6	37.8 ± 6.3
Phenotype	RR MS	RR MS

RR MS – relapsing-remitting multiple sclerosis; SD – standard deviation.

Image acquisition

The brain MRI examinations were performed with a 3T magnet (General Electric, Signa HDxt 3T, Milwaukee, WI, USA) with a standard 8HR head-coil. The MRI protocol included the following sequences: (1) T1-weighted (T1W) images with a repetition time (TR) of 30 ms and an echo time (TE) of 6 ms, a field of view of 250 mm, and a flip angle of 27°; (2) T2-weighted (T2W) Fluid-Attenuated Inversion Recovery (FLAIR) images with a TR of 9,000 ms and a TE of

83 ms, the field of view of 250 mm, and flip angle of 90°; (3) T2W images with a TR of 5,300 ms and a TE of 85 ms, field of view of 250 mm, and flip angle of 90°. Three-millimeter-thick contiguous slices were obtained. MRI scan was performed before and after the injection of linear gadolinium contrast agent (gadopentetate dimeglumine – Magnevist®) at 0.2 mL/kg of body weight.

Image analysis

Pre-contrast T1W MRI from the initial scan, and a scan ten years later, after follow-up, were used for analysis.

Analysis of pre-contrast T1W images was first utilized to define regions of interest (ROIs). ROIs included 16 anatomical regions of the brain: cortex of the frontal, temporal, parietal, and occipital lobes, *nucleus caudatus* (NC), *putamen*, thalamus, anterior and posterior horn of the internal capsule, *genu* and *splenium* of the *corpus callosum* (CC), *substantia nigra* (SN), *pons*, white matter of *centrum semiovale* (CSO), the white matter of *corona radiata* (CR), and cerebellar hemisphere (Figure 1).

The selection of voxels representative of cerebrospinal fluid (CSF) signal intensity (SI) consisted of starting inferiorly and moving superiorly on axial slices until the initial appearance of both anterior horns of the lateral ventricles and was used to determine the "CSF intensity" for CSF for that scan (Figure 2).

Two radiologists, with ten and nine years of experience in MS neuroimaging, respectively, conducted the quantitative analysis using a software package Carestream Vue PACS v 11.04.0 (Carestream Health, Inc., Rochester, NY). They were both blinded to the data. Both of them used the T1W images with previously defined ROIs and CSF to measure SI value. The SI value within any particular area was divided by the mean SI within the CSF to calculate the area-to-CSF SI ratio (Figures 1 and 2). In the event of disagreement in evaluating data, the radiologists reached a final consensus together.

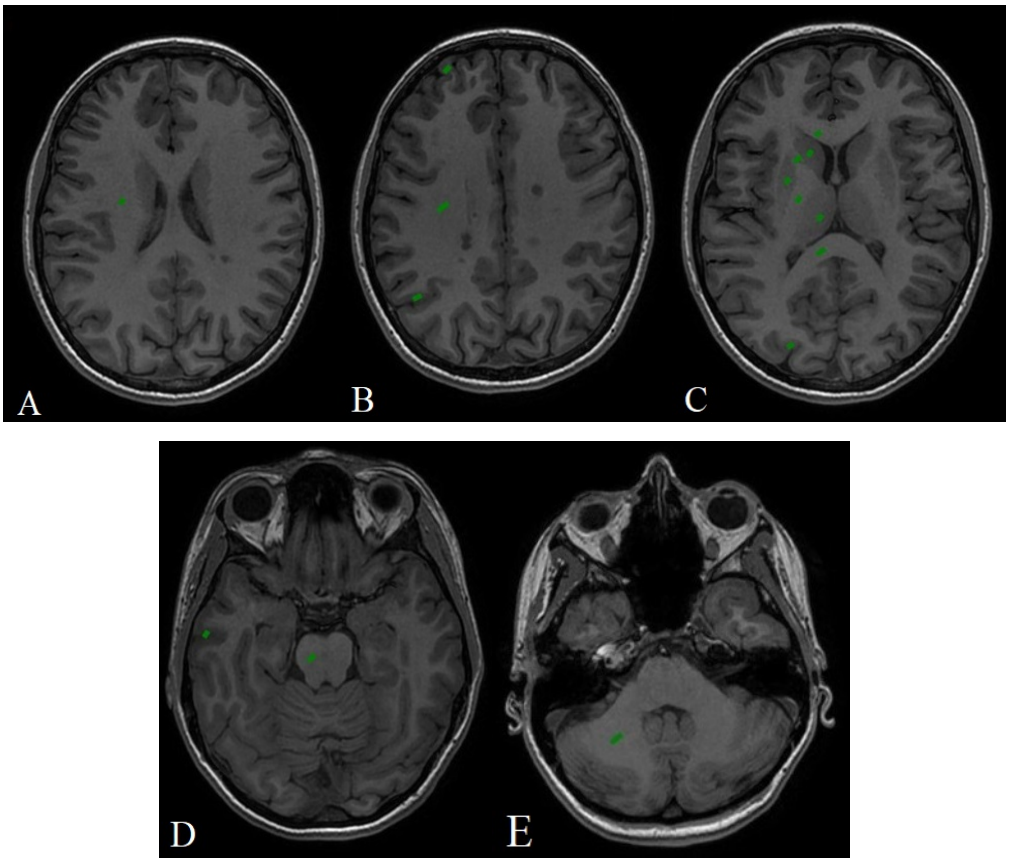

Fig. 1– Pre-contrast T1-weighted magnetic resonance images in a 50-year-old man with multiple sclerosis at the initial scan. Standard regions of interest were set in 16 different anatomical regions of the brain: the white matter of *corona radiata* (A), cortex of the frontal and the parietal lobes, white matter of *centrum semiovale* (B), cortex of the occipital lobes, *nucleus caudatus*, putamen, thalamus, anterior and posterior horn of the *capsula interna*, *genu* and *splenium* of the *corpus callosum* (C), cortex of the temporal lobes, *substantia nigra*, *pons* (D), and cerebellar hemisphere (E).

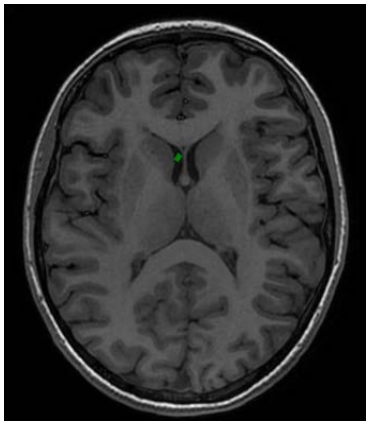

Fig. 2 – The signal intensity (SI) value in any given area is divided by the SI value of cerebrospinal fluid (CSF) within the anterior horns of the lateral ventricle to calculate the SI area-to-CSF ratio.

Statistical analysis

Statistical analysis was performed using the statistical software package PASW Statistics 18® [SPSS (Hong Kong) Ltd., Hong Kong]. All variables were presented as frequencies of certain categories. Continuous variables were presented as mean ± standard deviation and compared using paired *t*-tests.

Results

In the initial pre-contrast T1 images, the white matter of the CSO (1.744 ± 0.089), CC *genu* (1.734 ± 0.124), the anterior limb (1.765 ± 0.102), and posterior limb (1.723 ± 0.141) of the *capsula interna* (CI) had the highest values of the area-to-CSF SI ratio, and the lowest values of the area-to-CSF SI ratio were in SN, parietal cortex, temporal cortex, *pons*, and white matter of CR. After ten years, the anterior and posterior limb of the CI, CC *genu*, frontal cortex, and white matter of the CSO had the highest value of area-to-CSF SI ratio, while SN (1.399 ± 0.159), parietal cortex (1.496 ± 0.107), *pons* (1.505 ± 0.156), and temporal cortex (1.512 ± 0.141) had the lowest values. Comparing the value area-to-CSF SI ratio relationship from the initial and final MRI examination, there was a statistically significant difference in the frontal cortex ($p < 0.01$), occipital cortex ($p < 0.01$), and the white matter of the CR ($p < 0.01$) while parietal cortex ($p < 0.05$), thalamus ($p = 0.051$), *putamen* ($p = 0.06$), and anterior and posterior limb of the CI ($p = 0.062$) were close to statistical significance (Table 2).

Table 2

Comparison of the value of brain region-to-cerebrospinal fluid signal intensity ratio relationship from the initial and final magnetic resonance imaging (MRI) examination

Region of the brain	Initial MRI scan	Final MRI scan	*p*-value
Frontal cortex	1.674 ± 0.096	1.768 ± 0.142	<0.01
Parietal cortex	1.496 ± 0.107	1.559 ± 0.142	<0.05
Temporal cortex	1.512 ± 0.141	1.545 ± 0.143	0.375
Occipital cortex	1.601 ± 0.136	1.718 ± 0.188	<0.01
Putamen	1.674 ± 0.105	1.738 ± 0.086	0.06
Thalamus	1.595 ± 0.118	1.678 ± 0.102	0.051
Nucleus caudatus	1.605 ± 0.113	1.668 ± 0.098	0.091
Anterior limb of *capsula interna*	1.765 ± 0.102	1.837 ± 0.112	0.062
Posterior limb of *capsula interna*	1.723 ± 0.141	1.809 ± 0.110	0.062
Corpus callosum genu	1.734 ± 0.124	1.782 ± 0.112	0.241
Corpus callosum splenium	1.579 ± 0.176	1.644 ± 0.106	0.158
White matter of *centrum semiovale*	1.744 ± 0.089	1.763 ± 0.098	0.444
White matter of *corona radiata*	1.535 ± 0.129	1.627 ± 0.106	0.01
Pons	1.505 ± 0.156	1.560 ± 0.124	0.163
Substantia nigra	1.399 ± 0.159	1.472 ± 0.106	0.73
Cerebellar hemisphere	1.674 ± 0.111	1.694 ± 0.115	0.556

All values are expressed as mean ± standard deviation.

Table 3
The number of patients that had an increase in the value of brain region-to-cerebrospinal fluid signal intensity ratio at the initial and final magnetic resonance imaging scan

Region of the brain	Patient
Frontal cortex	15 (75)
Parietal cortex	13 (65)
Temporal cortex	11 (55)
Occipital cortex	15 (75)
Putamen	13 (65)
Thalamus	12 (60)
Nucleus caudatus	12 (60)
Anterior limb of *capsula interna*	13 (65)
Posterior limb of *capsula interna*	12 (60)
Corpus callosum genu	11 (55)
Corpus callosum splenium	13 (65)
White matter of centrum semiovale	10 (50)
White matter of *corona radiata*	9 (45)
Pons	13 (65)
Substantia nigra	12 (60)
Cerebellum hemisphere	15 (75)

All values are expressed as numbers (percentages).

By comparing the initial and final values of the SI ratio in each subject for each of the previously defined areas, we registered an increase in the value of the SI ratio in all subjects. The lowest (45%) percentage of respondents had an increase in the SI ratio of the white matter of CR and white matter of CSO (50%); the largest (75%) percentage of respondents had an increase in the SI ratio in the frontal cortex, occipital cortex, and cerebellar hemisphere (Table 3).

Discussion

GBCAs are widely used in MRI. They were first applied in 1988, and today, they are used in about 30% of MRI diagnostics [2].

They have long been considered safe to use; however, in 2006, cases of potentially lethal NSF caused by using GBCAs in patients with renal insufficiency were described [12, 13]. Then in 2014, Kanda et al. [5] published a paper on the intracranial accumulation of gadolinium, based on observations of the increased intensity of T1W signals in the ND and GP. Subjects receiving gadopentetate dimeglumine or gadodiamide had a statistically significant increase in SI in these structures. This study was subsequently confirmed through independent studies, in which an increase in T1W signal was also observed after intravenous administration of linear GBCAs. Namely, according to the structure of chelated ligands, GBCAs were divided into two groups, linear and macrocyclic [14, 15]. Since gadolinium itself is toxic, GBCAs were used in the form of chelating compounds bound to different ligands [15].

It is generally accepted that, due to their structure, macrocyclic GBCAs are more stable than linear GBCAs; therefore, there is none of the so-called degeneration of gadolinium, which can result in toxic effects, primarily on the kidneys, through which gadolinium is metabolized [16]. In the study by Ramalho et al. [8], gadolinium deposition in NC and GP after using linear GBCAs was confirmed.

However, the high SI in GP and NC in the T1W sequence can be observed in several diseases and conditions. Thus, for instance, the hyperintensity of T1W in NC is found in conditions such as calcifications of the basal ganglia after radiotherapy, Langerhans' histiocytosis, and MS. On the other hand, hyperintense GP in T1W is associated with liver dysfunction, Wilson's disease, exclusively parenteral nutrition, neurofibromatosis type 1, manganese toxicity, Randu-Osler-Weber disease, hemodialysis, and other health conditions that can cause calcification of GP, which should be kept in mind when interpreting the results of the study [5, 17–20].

In addition to gadolinium deposition in these two regions, deposition in other regions of the brain but of lower intensity has also been proven [21]. Among others, Zhang et al. [22] analyzed patients, each of whom had more than 35 applications of linear GBCAs. They found T1 hyperintensity not only in the ND (100%) and GP (100%) but also in SN (100%), the latter part of the thalamus (92%), *nucleus ruber* (77%), *colliculus* (77%), upper cerebellar peduncle (54%), NC (31%), whole thalamus (23%), and *putamen* (15%).

The results of our retrospective study on 20 patients with a diagnosis of MS were homogenized according to the therapeutic protocol and to the fact that all patients underwent MRI on the same machine with a magnetic field strength of 3T, which included the administration of a linear contrast agent (gadopentetate dimeglumine – Magnevist®), from 2010 to 2019, once a year on average. The pre-contrast T1W SI was measured by the anatomical structures, which were then divided by the SI of the right lateral ventricle to normalize the results, obtaining the SI ratio. The same methodology was used in similar research [5, 20, 23–25].

A statistically significant increase in signals was obtained in the structures: frontal, parietal, and occipital cortex, as well as supratentorial white matter. We should not neglect the results that are very close to statistical significance, such as the case of the thalamus $p = 0.051$, *putamen* $p = 0.06$, and CI $p = 0.062$.

We also analyzed the absolute increase in the value of SI in each patient. Thus, an increase in T1W SI was detected in 75% of patients in the frontal and occipital cortex and in the infratentorial white matter. In 65% of patients, an increase in the intensity of T1W signals was also observed in the parietal cortex, *putamen*, anterior limb of the CI, *splenium* of the CC, and *pons*. An increase in T1W SI was found in 60% of patients in the following regions: thalamus, NC, posterior limb of the CI, and SN. In 55% of patients, we detected signal enhancement in both the temporal cortex and the *genu* of the CC. In half of the patients, the signal amplification was registered in the white matter-CS and in 45% in the supratentorial white matter. In our study, the following structures were not examined: NC, *colliculi*, and *pedunculus cerebellaris* superior, while the thalamus was examined as a whole.

If we observed the increase of the signal in absolute values of the T1W signal, we might notice that it was increased in the frontal and occipital cortex and infratentorial white matter in three-quarters of patients. A slightly smaller increase in SI, but still greater than 55–65%, was registered in structures such as the parietal cortex, *putamen*, anterior and posterior limb of the CI, *splenium* of the CC, *pons*, thalamus, NC, SN, and the temporal cortex.

Thus, it has been shown that after long-term use of gadolinium in patients diagnosed with MS, the absolute values of the T1W signal are registered not only in the basal ganglia but also in other areas. However, things can be viewed from another angle. Since MS is a diffuse disease that predominantly affects white matter, contrast deposition in these zones was registered in 55% and 45% of respondents, which may suggest that these brain regions are most affected by the underlying disease, unlike cortical structures that are less affected by MS. Research has shown that gadolinium deposition occurs in other diseases and in patients who do not have intracranial diseases [5, 17–20, 26].

In this study, the linear GBCA was used. In retrospective studies involving patients with recurrent linear GBCAs, changes in T1 signaling in the basal ganglia correlated with the number of linear GBCAs such as gadodiamide and gadopentetate [27, 28]. Subjects received gadopentetate dimeglumine (Magnevist®), a linear GBCA, for the duration of the study. On the other hand, some studies focused on examining changes in SI in patients who received multiple macrocyclic GBCA gadobutrol (Gadovist®), gadoterate meglumine, and gadoteridol, which were more stable, and found that macrocyclic GBCA was not associated with significant changes in SI in GP and NC [26, 27]. Studies comparing linear (gadopentetate) and macrocyclic (gadoteridol or gadoterate meglumine) agents have confirmed that changes in SI are significantly and exclusively associated with the use of linear agents [28].

What the results of our study, as well as many other studies, open as a topic for new research, is whether the intracranial deposition of gadolinium in different structures is proven since its toxicity is known and which implications that may have. Little is known about the clinical consequences of intracranial gadolinium deposition.

Thus, one study dealt with parkinsonism as a possible consequence of gadolinium deposition, taking into account that a significant percentage showed gadolinium deposition in GP, from which it could be concluded that gadolinium deposition should be associated with extrapyramidal dysfunction and with parkinsonism.

In a population study (n = 246,557) of two groups, who underwent MRI, between 2003 and 2013 (one group exposed to at least one dose of GBCA and the other without exposure), the authors did not find a significant difference in the presence of accidental parkinsonism and concluded that their results contradict the hypothesis that gadolinium deposits in GP lead to neuronal damage that manifests as parkinsonism [29, 30].

Semelka et al. [6] proposed a new category of disease – gadolinium deposition disease, based on an observational study of 42 patients who had previously undergone MRI with GBCA. In the acute phase of gadolinium exposure, patients complained of central and peripheral pain, headache, bone pain, and skin thickening. In the chronic phase, 29 of 42 patients had problems with concentration and headaches. Of course, all this could and should be the subject of further research.

MRI diagnostics are getting more and more common; however, ultrasound diagnostics is the safest and least harmful compared to other radiological procedures. Until recently, using gadolinium contrast agents was considered safe, but today, as the number of procedures increases, certain questions, which will certainly capture the attention of the professional public and deserve an answer, arise.

Retrospective analysis and a small number of patients are significant study limitations. Additional studies with a larger number of patients are necessary to validate our findings further.

Conclusion

The study showed that in a cohort of 20 patients, there was a statistically significant increase in SI in the T1W sequence in the following structures: frontal, parietal, and occipital cortex, as well as supratentorial white matter.

An increase in the absolute values of the T1W signal in three-quarters of patients was registered in the frontal and occipital cortex and cerebellar hemispheres. A slightly smaller increase in SI, but still greater than half (55–65%), was registered in structures such as the parietal cortex, *putamen*, *cornu* anterior and posterior of the CI, *splenium* of the CC posterior, *pons*, thalamus, NC, SN, *genu* of the CC, and temporal cortex.

This result speaks in favor of the existence of chronic accumulation of gadolinium contrast agent gadopentetate dimeglumine. We can also conclude from the research that the white brain matter of the CR and the CSO are most affected by the disease itself.

Since all subjects in our study suffered from an RR form of MS, we cannot distinguish with certainty the effects of the underlying disease from the potentially harmful effects of contrast agent accumulation.

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