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T1 signal intensity changes in dentate nucleus and lentiform nucleus on unenhanced T1-weighted MR images after intravenous administration of linear and macrocyclic contrast gadolinium based agents

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ABSTRACT

Purpose: Our aim is to establish a connection between intravenous injections of gadolinium based contrast agents (GBCAs) and T1 signal intensity increase in dentate nucleus and lentiform nucleus.

Material and Methods: The population of the study consisted of 166 patients who underwent brain MRI (456 total MRI scans) after IV injection of a gadolinium based contrast agent (linear: Gadodiamide, Gadopentetic acid/ Gadopentate dimeglumine and macrocyclic: Gadoteric acid, Gadobutrol), at least twice between September 2013 and April 2017, and a control group which consisted of 50 patients who had never received GBCAs intravenously. Signal intensity was measured in the lentiform nucleus and dentate nucleus bilaterally on unenhanced T1weighted images for all the groups. Statistical analysis of the acquired measurements was performed.

Results: Patients who received Gadodiamide presented a mean T1 signal increase of 46.5 units (to SD ± 74) of the initial dentate nucleus signal; compared the control group the difference was statistically significant (p=0.034). A statistically significant T1 signal increase in lentiform nucleus is associated to administration of Gadobutrol, with a mean

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signal intensity increase of 23.6 units (SD ± 47.9) and statistical significance (p=0.43). No increase in signal intensity was noted for Gadoteric acid and Gadopentetic acid.

Conclusions: Intravenous administration of Gadodiamide and Gadobutrol results in signal intensity increase in lentiform nucleus and dentate nucleus.

KEY WORDS

Magnetic Resonance Imaging; Gadolinium; Contrast media; Dentate nucleus; Lentiform nucleus

1. Introduction

Gadolinium (64Gd) is a rare metal used in contrast agents for Magnetic Resonance Imaging (MRI), because of its ability to alter the longitudinal relaxation time of nearby water molecules by interacting with their unpaired electrons. In its free form gadolinium, is highly toxic and it shows a slow excretion rate. In order for gadolinium to be used as contrast agent it needs to be bonded with chelating agents, preventing contact of free gadolinium with body tissues and facilitating renal excretion, maintaining its paramagnetic properties [1].

Gadolinium based contrast agents (GBCAs) are divided into two main categories, according to their chemical structure: linear GBCAs and macrocyclic GBCAs. Macrocyclic GBCAs differ from linear GBCAs in that gadolinium ions in macrocyclic GBCAs are isolated in a rigid cavity. As a result, the degradation rate for macrocyclic GBCAs is lower, therefore the release of free gadolinium ions in systemic circulation is less [2]. Despite the stability difference between macrocyclic and linear GBCAs, both are used in everyday practice, as they are considered adequately stable for patients with normal renal function.

Lately however new questions are raised over the safety of intravenous (IV) injection of linear GBCAs, because it has been observed in several studies (Kanda et al, Errante et al) [3, 4] that repeated administration of linear GBCAs (Gadodiamide, Gadopentetic acid) leads to gradual increase of signal intensity in the dentate nucleus in unenhanced T1 weighted (T1W) images, in patients with normal renal function. A number of studies [5-7] over macrocyclic GBCAs (Gadoteric acid, Gadobutrol) did not show significant increase in signal intensity in the dentate nucleus and lentiform nucleus, while other studies [8, 9] revealed the opposite.

Our goal is to clarify whether IV administration of certain macrocyclic and linear contrast agents leads to increase in signal intensity in the dentate nucleus and lentiform nucleus.

2. Materials and Methods

This study was approved by the institutional review board of our Hospital.

2.1 Patient selection

Patients were selected retrospectively from the Medical Reports Database of the MRI department of "George Papanikolaou" General Hospital of Thessaloniki, Greece. The study population consists of 216 patients in total. We included 166 patients that underwent multiple brain MRI scans with IV injection of a paramagnetic contrast agent (macrocyclic or linear) at least once, from September 2013 to April 2017. Despite the short half-life of GBCAs [10], we set a minimum interval time of 10 months between MRI scans to ensure maximum renal excretion of the IV administered gadolinium.

Additionally we formed prospectively a control group which consisted of 50 patients in whom no paramagnetic contrast agent had been administered before.

2.2 Image Acquisition

All MR images in this study were acquired at a Siemens Magnetom Symphony Maestro Class 1.5 T scanner (Siemens Healthcare, Erlangen, Germany). Each brain MRI scan protocol included unenhanced and enhanced axial T1W images. The following imaging parameters were used: TR 350-600ms; TE 7-9ms; echo train length 1; flip angle 90 degrees; matrix 256x168, 256x156, 256x144; section thickness 5 mm; number of excitations 1.

2.3 Image analysis

MR images and data were extracted from G. Papanikolaou Hospital's Picture Acquisition and Communication System (PACS). Image analysis was performed on a Siemens workstation, using Syngo MR A35 4VA35A software. Unenhanced T1W axial images were used. Quantitative analysis was performed by placing circular regions of interest at both left

Table 1. Mean dentate and lentiform nucleus signal change and standard deviations (SD) in patients who received or did not receive a given contrast agent

Contrast Types		*Dentate Nucleus Signal Change*	*Lentiform Nucleus Signal Change*
Gadoteric Acid	No	-1.95 (SD 76.7)	6.4 (SD 57.4)
	Yes	-3.39 (SD 83.4)	1.8 (SD 64.1)
Gadobutrol	No	-5.8 (SD 80.7)	0.1 (SD 62.1)
	Yes	12 (SD 72)	23.6 (SD 47.9)
Gadopentetic Acid	No	1.3 (SD 71.4)	5.5 (SD 53.2)
	Yes	-3.8 (SD 82.9)	4.7 (SD 63.4)
Gadodiamide	No	-5.6 (SD 78.5)	2.5 (SD 60.6)
	Yes	46.5 (SD 74)	36 (SD 42.3)

and right dentate nucleus (0.3 cm^2 area) and left and right lentiform nucleus (0.5 cm^2 area) to measure mean signal intensity. A mean signal intensity value between left and right was calculated. Additionally axial T2W images were used to facilitate visual recognition of the aforementioned anatomical regions whenever necessary.

3. Results

3.1 Rational of data analysis

Statistical analysis was conducted using the IMB SPSS Statistics 20 Software. A total number of 166 patients (71 male, 95 female) were retrospectively selected from our department's database using the criteria described in the Materials and Methods section. All patients were subjected to MRI imaging two or more times and received a contrast agent at least once. Sixty six patients (39.8%) received Gadoteric acid, 34 patients (20.5%) receiver Gadobutrol, 111 patients (66.9%) received Gadodiamide and 12 patients (7.2%) received Gadopentetic acid. Some patients received more than one type of contrast agent whereas some patients received the same contrast more than once. Specifically, 95 patients received GBCA once, 37 patients twice, 27 patients three times, 3 patients four times and 4 patients five times. One hundred thirteen patients received the same GBCA and 53 patients received more than one type of GBCA.

In order to simplify our statistical analysis we decided to consider only two T1 signal measurements for the dentate nucleus and two T1 signal measurements for the lentiform nucleus, which were the T1 signal before contrast injection on the first MRI and the T1 signal before contrast injection on the last MRI. From those values we then calculated the T1 before contrast signal change between first and last MRI examination at the level of the dentate and lentiform nucleus and investigated whether the change amplitude is related to each given contrast agent. Given that we included patients that were subjected to more than one contrast enhanced MRI scans and patients that received more than one type of contrast, we decided to first examine each contrast agent separately and then construct (if necessary) a multilinear regression model. By this way we could consider the T1 signal change (dependent variable) in relation to a combination of contrast agents (independent variables) and investigate for collinearity and confounding between them.

3.2 Findings

The T1 pre contrast signal change of the dentate and lentiform nucleus between first and last MRI examination in patients who received and patients who did not receive a certain contrast agent is shown in **Table 1**.

Dentate nucleus

Unifactorial analysis of dentate nucleus signal change for each administered contrast agent revealed statistical sig-

Table 2. Comparison of dentate and lentiform nucleus signal change between patients that received Gadodiamide and patients that did not receive Gadodiamide

	Gadodiamide No	*Gadodiamide Yes*	*Mean Difference and 95 % CI*	*p value*
Dentate Nucleus Signal Change	-5.6 (78.5)	46.5 (74)	-52.1 (-100.4, -3.9)	0.034
Lentiform Nucleus Signal Change	2.5 (60.6)	36 (42.3)	-33,4 (-68.7, 1.8)	0.063

Table 3. Multiple linear regression for lentiform nucleus signal change and Gadobutrol and Gadodiamide as independent variables

Regression for Lentiform Nucleus Signal Change			
Contrast Type	B	Std. Error	p value
Gadobutrol	22.8	11.3	0.046
Gadodiamide	32.4	17.7	0.069

Table 4. Comparison of dentate nucleus signal intensity between control group and patients who received Gadodiamide

	T1 Signal Intensity of Dentate Nucleus	Mann-Whitney
Control Group	273 (IQ 61)	p=0.029
Non-Control Group who received Gadodiamide	320 (IQ 125)	

Table 5.Comparison of lentiform nucleus signal intensity between control group and patients who received Gadodiamide and Gadobutrol

	T1 Signal Intensity of Lentiform Nucleus	Mann-Whitney
Control Group	259 (IQ 51)	p=0.1
Non-Control Group who received Gadodiamide	300 (IQ 77)	
Non-Control Group who received Gadobutrol	276 (IQ 77)	p=0.072

nificant findings for Gadodiamide. Patients who received Gadodiamide presented a mean T1 signal increase of 46.5 units (SD ± 74) which corresponds to 18.1% increase (SD ± 27%) of the initial dentate nucleus signal.

Patients who did not receive Gadodiamide presented a mean signal change of -5.6 units (SD ± 78.5). The difference between the two groups was statistically significant (p=0.034, **Table 2**).

Lentiform nucleus

Gadodiamide administration is also associated to lentiform nucleus T1 signal increase. Patients who received Gadodiamide presented a mean T1 signal increase of 36 units (SD ± 42.3) or 14% increase (SD ± 16.8%) as compared to the initial signal intensity. In patients who did not receive Gadodiamide the mean signal increase was only 2.5 units (SD ± 60.6). The difference between the two groups is close to the level of statistical significance 0.05 (p=0.063, **Table 2**).

Unifactorial analysis for lentiform nucleus also revealed a statistically significant T1 signal increase associated to administration of Gadobutrol. Patients who received Gadobutrol presented a mean signal intensity increase of 23.6 units (SD ± 47.9) which corresponded to 10.8% (SD ± 19.1) increase of initial value. The difference compared to patients that did not receive this contrast agent was found to be statistically significant (p=0.042), with mean difference and 95% CI -23.4 (-46, -0.8).

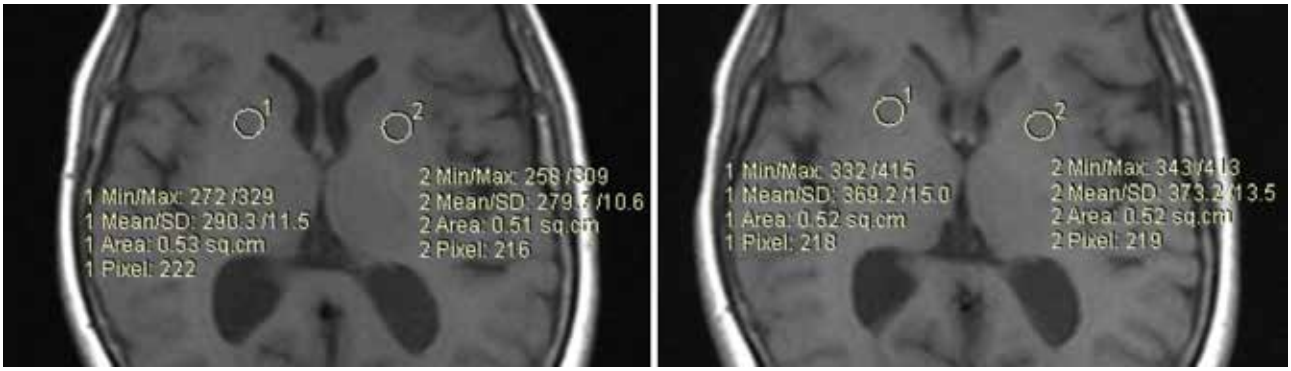

Fig. 1. *T1 signal intensity increase in the lentiform nucleus, one year following IV administration of linear GBCA.*

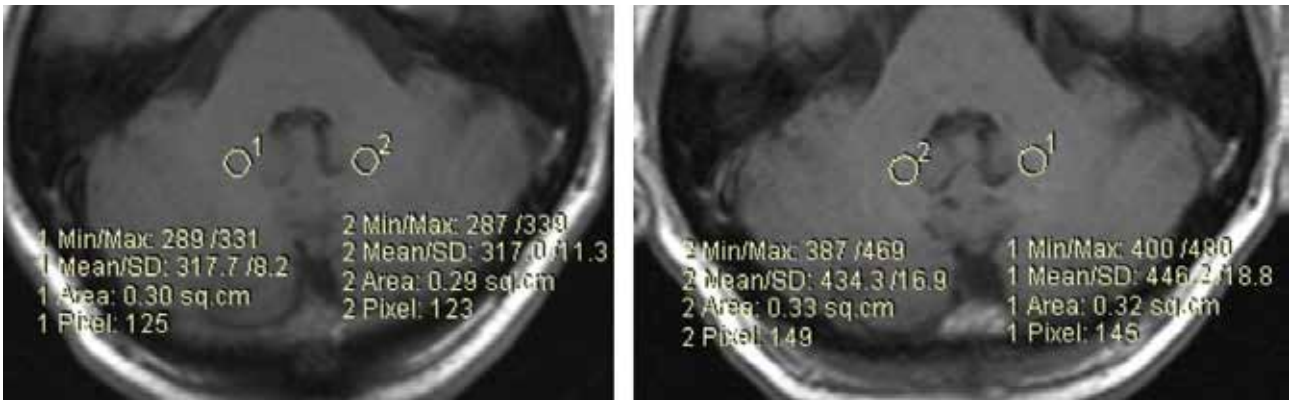

Fig. 2. *T1 signal intensity increase in the dentate nucleus, one year following IV administration of Gadobutrol.*

Multilinear regression analysis

In order to investigate for possible collinearity and confounding between the two contrast agents that were found to increase the signal of lentiform nucleus we calculated the Kendall's correlation coefficient between Gadodiamide and Gadobutrol use (Kendall's b 0.31, p value 0.68) and we also tested those contrast agents in a multilinear regression model with lentifom nucleus signal change as independent variable (**Table 3**). As shown, there is no correlation between the use of the two contrasts and p values of regression remain almost invariable as compared to unifactorial analysis.

Control group

Given the limitations related to the retrospective nature of our study design with unavailable data from some participants, we decided to prospectively select a control group of patients that were subjected to MRI imaging in our department and from whom full medical history was obtained.

The control group was composed of 50 patients (28 male, 22 female). Only patients that had never before been subjected to MRI imaging were enrolled. The T1 signal of the dentate and lentiform nucleus were measured and then compared to the T1 signal of the last MRI of patients that had a history of contrast enhanced MRI (the retrospective part of our study). The results are shown in **Tables 4 and 5**.

As demonstrated in the tables, patients with a history of Gadodiamide administration presented a higher T1 signal intensity in the dentate nucleus compared to the control group and the difference was statistically significant (p=0.029). The signal intensity was also higher in the lentiform nucleus but this was not found to be statistically significant (p=0.1).

Finally patients with a history of Gadobutrol administration presented a higher lentiform nucleus T1 signal intensity compared to the control group and the difference was close to the level of statistical significance 0.05 (p=0.072).

It is worth mentioning that in some patients the increase in T1 signal intensity in the dental nucleus and lentiform nucleus was visible to the radiologist without using the ROI. However we did not include these findings, as our study was quantitatively oriented.

4. Discussion

The results of this single-center retrospective study based on a large number of patients demonstrate correlation

between a high-signal intensity dentate nucleus and lentiform nucleus on T1W images in patients with a history of Gadodiamide administration. Furthermore a correlation between a high-signal intensity lentiform nucleus and previous Gadobutrol administration is revealed. No such relationship was established for Gadoteric acid and Gadopentetic acid. These results take place in the absence of severe renal and hepatobiliary dysfunction. All our patients had normal renal and hepatic function at the beginning and end of the study.

As far as Gadodiamide is concerned, our findings complement the MR signal intensity changes in dentate nucleus and basal ganglia (specifically the lentiform nucleus in our study) observed by McDonald et al [11] and Kanda et al [12]. McDonald et al [11] correlated the radiological findings with gadolinium deposition in neuronal tissue samples, using mass spectrometry and transmission electron microscopy. Gadodiamide IV administration is related to signal intensity increase in lentiform nucleus and dentate nucleus. By using control patients our findings suggest that the high signal intensity of the dentate nucleus and lentiform nucleus on T1W images are specific to Gadodiamide administration. Zhang et al [13] revealed a relationship between linear GBCAs administration and T1 signal increase in globus pallidus and dentate nucleus, although they examined several linear GBCAs (Gadodiamide, Gadopentate Dimeglumine and Gadobenate) together and not the impact of Gadodiamide alone.

As for Gadobutrol, our study demonstrated a statistically significant correlation between increase in MR signal intensity in the lentiform nucleus on T1W images and the administration of Gadobutrol. In the dentate nucleus on the other hand there was no statistically significant T1 signal increase, in keeping with the results Radbruch et al [14] provided. Stojanov et al [8] did see a correlation between Gadobutrol administration and MR signal increase in globus pallidus and dentate nucleus, although their study was limited to patients with relapsing-remitting multiple sclerosis. According to them, T1 hyperintensity of the globus pallidus and dentate nucleus seen in patients with multiple sclerosis may have more to do with repeated gadolinium based contrast agent administrations than the disease itself.

Intravenous administration of Gadopentetic acid showed no significant MR signal increase in the dentate nucleus and lentiform nucleus. However the number of patients that underwent MRI brain scans before and after IV injection of Gadopentetic acid in our study is limited, so no safe conclusion can be safely drawn on the matter.

Our study confirms the results of Radbruch et al [6] regarding Gadoteric acid. Patients who had been injected with Gadoteric acid showed no significant increase in MR signal in the dentate nucleus and lentiform nucleus.

Conclusively these results contradict the conviction [3, 6, 15] that the use of linear GBCAs alone leads to signal intensity increase, as Gadobutrol which is a macrocyclic agent, in our study, is also correlated to MR signal increase in the lentiform nucleus.

Our study has several limitations. Because this is a retrospective study, there were variations (however slight) in TR and TE times between the MR scans which might be a confounding factor. To minimise this effect we selected MRI scans with narrow TR and TE value range. Furthermore all selected scans were acquired by the same MRI scanner.

The patients' clinical history was not always available and for that reason the change of T1 signal intensity between two consecutive examinations was appreciated and not the initial value.

A correlation between radiologic and pathologic findings could not be made. In some cases it was uncertain whether GBCAs had been administered between MRI scans, as it was identified solely based on our database.

Our data suggest that a differentiation between macrocyclic and linear GBCAs may not be enough to prognosticate whether signal intensity will increase or not [2], but more variables have to be taken into account. The mechanisms by which gadolinium administration causes high MR signal intensity in the dentate nucleus and the lentiform nucleus remain obscure. Moreover the clinical implications of the increase in signal intensity still remain unclear [16]. Smith et al [17] conducted a literature review to find a correlation between administration of GBCAs and possible health outcomes, but no clear evidence was found.

Further investigation needs to be done and if possible to correlate with clinical significance.

5. Conclusions

Intravenous administration of Gadodiamide and Gadobutrol results in signal intensity increase in the lentiform nucleus and dentate nucleus. Patients who received Gadoteric acid showed no signal intensity increase in the dentate nucleus and lentiform nucleus. R

Conflict of interest

The authors declared no conflicts of interest.

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