

Preliminary Study of Gadolinium Accumulation in Gliai Tumours of Human Brain

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Abstract: The aim of our study was to directly determine the accumulation of gadolinium in glial brain tumors after a single intravenous injection of an MRI contrast agent Magnevist. Study was carried out on samples of glial tumours of human brain extracted during standard brain surgery. The samples from five patients with glial tumours and single Magnevist intravenous injection for MRI in different times before surgery were studied. Samples of two patients with glial tumours and without intravenous administration of Magnevist and other gadolinium containing compounds were studied as control. Gadolinium content in tumour tissues was analyzed by method of neutron activation analysis. It was found that in all five investigated samples gadolinium present in concentrations from 0.0093 to 0.2384 ng/mg (ppm) tumour tissue. In control samples, the gadolinium has not been detected. The correlation between the Gd accumulation and the amount of Magnevist injection during MRI was observed. At present time, the clinical importance of detected effect of gadolinium accumulation in brain tumours after intravenous introduction of pharmacological chelate compounds of gadolinium is not clear enough. As free gadolinium is toxic, so the establishment of fact of gadolinium accumulation in brain tumours can appear significant for interpretation of various unexpected clinical effects in the future.

Keywords: clinical study, Magnevist, gadolinium accumulation, human brain glial tumours, neutron activation analysis, neutron-capture therapy.

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I. Introduction

Gadolinium-based contrast agents (GBCAs) have been widely used in clinical MR imaging studies. GBCAs differ in standard linear (ionic and non-ionic) and macrocyclic (ionic and non-ionic) properties [1]. These GBCAs are available for clinical use one or more in each region of the world. In each year, over 30 million doses of GBCAs are consumed worldwide, and more than 300 million doses have been administrated since their introduction [2]. It is known that, all GBCAs approved for clinical use have been considered to have a wide safety margin when used at relatively low doses (0.1–0.3 mmol/kg) in patients with normal renal function. Until 2006, all GBCAs were considered extremely safe. Clinically available GBCAs are all bonded by a ligand when they are used as an MRI contrast agent because free gadolinium is highly toxic [3]. MRI with GBCAs allows to detect wide variety of pathological processes [4-6]. In the work [7] was stated that some GBCAs may lead to NSF in patients with renal failure. However, when performing careful evaluation of the renal glomerular filtration rate before CE-MRI, new NSF cases have not been reported. Since 2013, the safety of GBCAs has attracted broad attentions over the world. A research group reported [8] that signal intensity in the GP and DN on unenhanced T1 weighted imaging (T1WI) may be a result of the previous GBCAs administrations. This phenomenon leads to reconsideration of the safety of GBCAs. Following this report, many studies [9-12] focused on the potential risks of gadolinium retention in the human brain. During the last years some studies were carried out showing accumulation of gadolinium in various parts of brain of patients after single and repeated administrations of gadolinium-containing preparation «Magnevist» [13]. Accumulation of gadolinium in globus pallidus, thalamus, dentate and pons has been shown. Also it has been shown that depositions of gadolinium remain during long time in tissues of human brain.

Most of the known toxicity of the free Gd³⁺ ion is related to 2 properties: its insolubility at physiologic pH, resulting in very slow systemic excretion; and an ionic radius close to that of Ca²⁺ (Gd³⁺ 107.8 pm and Ca²⁺ 114 pm) that allows Gd³⁺ to compete biologically with Ca²⁺ [13-14]. Gadolinium is a well-known blocker of many types of voltage-gated calcium channels at very low concentrations, and consequently, it can inhibit

physiologic processes such as contraction of smooth, skeletal, and cardiac muscles; transmission of nerve impulses; and blood coagulation. It also inhibits the activity of certain enzymes such as Ca^{2+} -activated- Mg^{2+} - adenosine triphosphatase, some dehydrogenases and kinases, and glutathione S-transferases. It also acts as an agonist on the calcium-sensing receptors[15]. Gadolinium may also increase the expression of some cytokines,[16] inhibit mitochondrial function, and induce oxidative stress.[17,18].

In last times, the number of studies on the use of Gd in radiotherapy to increase the radiosensitivity of tumors has increased. In accordingly, it is necessary to accurately calculate the amount of absorbed doses needed to determine the level of gadolinium in tumors, which are necessary for reliable knowledge of the presence of gadolinium in tumors accumulated due to intravenous administration of gadolinium-free contrast compounds for MRI diagnostics. In work [19] was found that, radiotherapy can induce R1 value increase in the brain parenchyma, which might suggest accelerated gadolinium accumulation due to damage to the blood-brain barrier.

Recently studies have confirmed gadolinium accumulation in human brain following repeated GBCA administrations, regardless of an intact BBB or normal renal function. Linear chelates GBCAs can result in more gadolinium deposition than macrocyclic chelates GBCAs. However, the impact of the retained gadolinium in the brain remains unknown, which needs large prospective studies to clarify in future. It is recommended to take caution when using macrocyclic chelates GBCAs and keep as low doses as possible for reducing gadolinium accumulation in brain [20].

In spite of rapidly increasing number of published articles, the knowledge on gadolinium deposition in the brain and its clinical significance is still insufficient. There exist many unsolved problems: 1) Whether the deposited gadolinium in the brain may result in any clinical consequences unreported during periods of study observation; 2) The mechanism of GBCA deposition in the brain remains unknown, and several related problems are still unsolved; 3) The mechanism of disease itself affecting the gadolinium deposition in the brain is still unknown. Future studies should focus on these unsolved problems and give valid evidences to the public. Therefore, we had been conducted small pilot study with aim to establish precisely amount of gadolinium accumulated in human brain tumours after single standard administration of Magnevist during MRI diagnostics of tumours. We believe that such studies provide important information to further improve the effectiveness of binary radiotherapy methods and to clarify the question of the influence of the disease mechanism on the deposition of gadolinium in glial tumors of the human brain.

II. Material and Methods

We carried out a pilot prospective study of gadolinium accumulation in the glial tumors of human brain after single intravenous administration of Magnevist. Because of small number of studied patients this pilot study does not allow the use of statistical methods of processing results. Despite of small number of data we suppose that found results are important enough for publication.

Criteria of patients enrolling. For study 5 patients with operable brain tumours, undergone one procedure MPI with Magnevist enhancing during various time before operation have been selected. For control group 2 patients with operable brain tumours, undergone procedure MPI without enhancing by gadolinium-containing preparations have been selected. The selected patients did not have any clinical symptoms of renal or hepatic insufficiency. For all patients MRI images have been collected.

Selection and preparation of samples. Operations of tumours extraction were spent under the general intubation narcosis. After craniotomy of skull the encephalotomy was made, then access to tumour was made. With application of microsurgical techniques it was made dissection of tumours from a brain tissue and removal of tumour by fragmentation. Part of extracted tumour fixed in 10 % formalin for standard histological analysis. From extracted fragments of tumours the samples were cut out and placed in pure glass vials and frozen in the refrigerator at -18°C without addition of saline solution or any other liquid.

All collected samples were weighed, then were freeze-dried and again weighed to determine dry weight of samples. The freeze-dried samples were analyzed with help of neutron activation analysis.

Neutron activation analysis of samples.

Preparation and irradiation of samples. Aliquots of 100 mg of freeze-dried samples were inserted in polyethylene bags, hermetic sealed and wrapped in aluminium foil. Prepared samples with reference sample were sealed in quartz ampoule and irradiated in vertical channel of nuclear reactor VVR-SM (INP, Tashkent). The neutron flux was 5×10^{13} n/(cm²sec). Samples was irradiated during 2 hours.

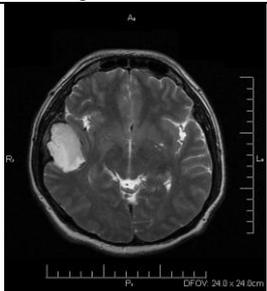
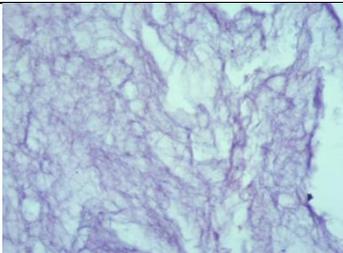
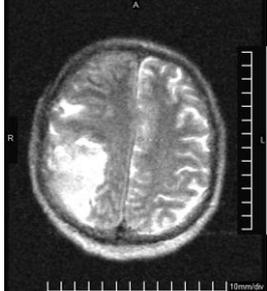
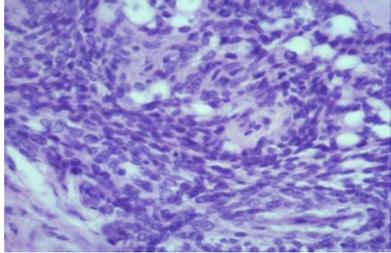
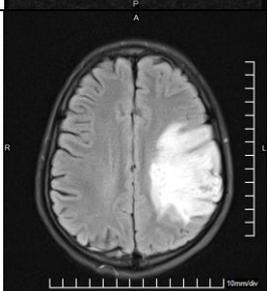
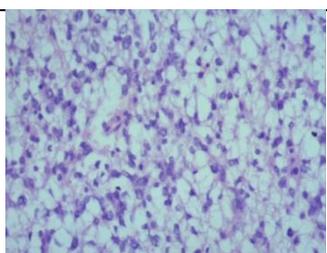
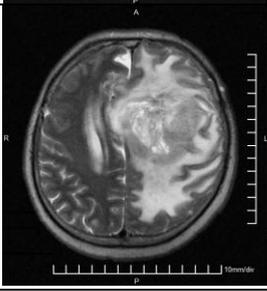
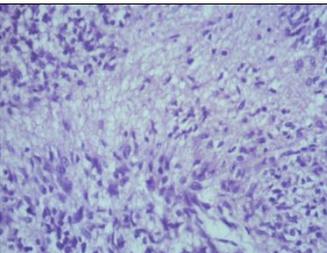
Preparation of reference sample. Reference sample was prepared with addition of known quantity of gadolinium in tissue sample, initially not containing gadolinium. For preparation of reference sample the commercial drug Magnevist with known gadolinium concentration was used.

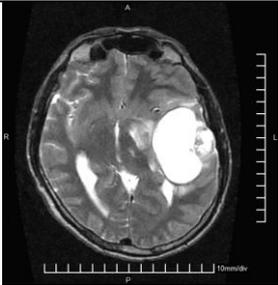
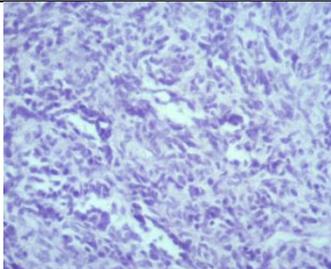
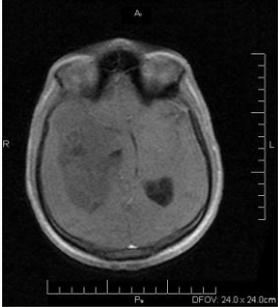
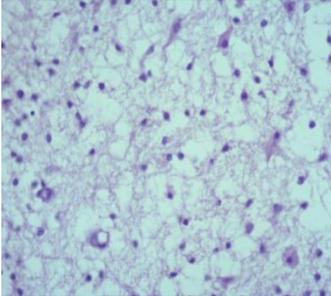
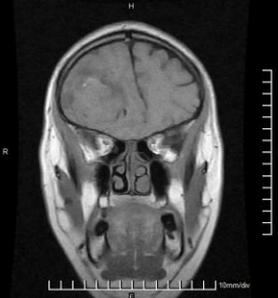
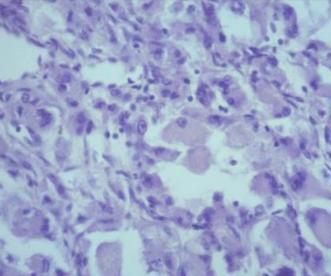
Activity measurements and calculation of gadolinium content. After irradiation samples were stored during 3 weeks, after that gamma-activity of radionuclides was measured with use of gamma spectrometer Canberra, equipped with high pure germanium semiconductor detector GC2018 and multichannel analyzer DSA1000. Measurements and spectra processing was carried out with use of Genie2000 software. For identification and calculation of gadolinium content the gamma lines of ^{153}Gd with energy 94.7 keV and 103.2 keV were used (Figure 1). Investigated samples and reference sample were measured in identical geometry. For calculation of gadolinium content the relative method was used.

III. Results

In study group were enrolled 5 male patients at the age from 30 to 58 years, and in control group were enrolled 2 male patients at the age 37 and 39 years. Clinical data of selected patients are presented in table 1.

Table 1. The diagnostic data of patients of study and control groups.

Patient №	MRI data	Histological diagnosis
STUDY GROUP –Magnevist enhanced MRI		
1		 Epidermoid cyst
2		 Metaplastic meningioma
3		 Fibrillary astrocytoma
4		 Glioblastoma astrocytic origin

5			Spindle cell glioblastoma
CONTROL GROUP – MRI without Magnevist enhancing			
6			Fibrillary astrocytoma
7			Giant-cell glioblastoma

Neutron activation analysis of samples. For determination of trace amount of gadolinium in ppm requires using of high sensitive analysis method. The best known and widely used for these purposes is mass spectrometry analysis method. However, we used neutron activation analysis method, which on number of detected elements and sensitivity is not inferior to mass spectrometry and even exceed in some parameters.

For determination of gadolinium content in investigated samples, the relative instrumental neutron activation method was used. Natural gadolinium consists of six stable isotopes, three of which undergo reaction (n, γ) and generate radioactive isotopes of gadolinium [21].

Table 2. Characteristics of some gadolinium isotopes.

Isotope	Content, %	Reaction	Radionuclide	Activation cross-section σ , barn	Resonance activation integral I, barn
Gd-152	0.2031	(n, γ)	Gd-153	735	2020
Gd-158	24.835	(n, γ)	Gd-159	2.2	73
Gd-160	21.863	(n, γ)	Gd-161	0.79	7.2

Table 3. Half-life of isotopes and energies of gamma lines.

Radionuclide	Half-life	Main gamma lines, keV	Output, %
Gd-153	240.4 days	69.7	2.4
		97.4	29.0
		103.2	21.1
Gd-159	18.5 hours	58.0	2.5
		363.5	11.8
Gd-161	3.66 minutes	102.3	13.9
		283.5	6.0
		314.9	22.7
		360.9	60.1

As shown in tables 2 and 3, taking into account half-life and gamma lines output at first sight the most convenient analytical radionuclide is Gd-159 with half-life period 18 hours. However, high content of

phosphorus in analyzed tissue samples and the high gamma background, resulting from generation P-32 makes it practically impossible determination of gadolinium on radionuclide Gd-159. Therefore for identification and amount determination of gadolinium as analytical radionuclide was used radionuclide ^{153}Gd ($T_{1/2} = 242$ d), which produced by reaction $^{152}\text{Gd}(n,\gamma)^{153}\text{Gd}$ with high activation cross-section and has gamma lines with energies 97.4 keV and 103.2 keV (Figure 1).

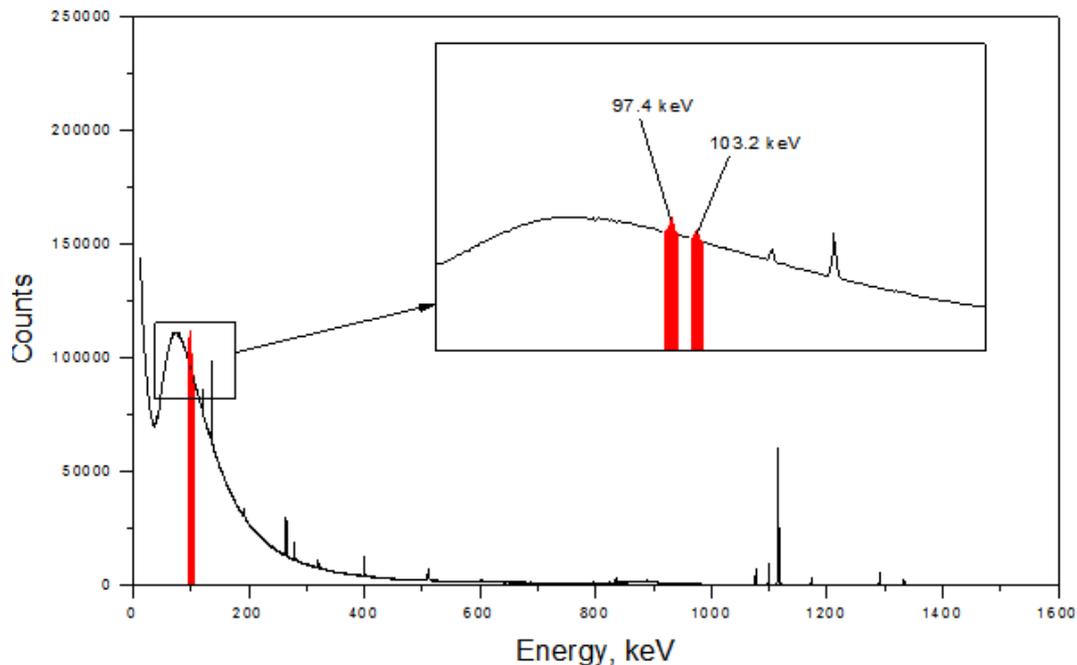


Figure 1. Gamma spectrum of tissue sample, irradiated by neutrons (irradiation time = 2 hours, neutron flux = 5×10^{13} n/(sm²sec), storage time = 3 weeks, measurement time = 3 hours).

We found that in all five investigated samples gadolinium present in concentrations from 0.0093 to 0.2384 ng/mg (ppm) tumour tissue. In control samples, the gadolinium has not been detected (see table 3).

Table 3. – The results of gadolinium concentration determination in samples of glial tumours of human brain by neutron activation analysis method.

No of patient	Crude weight of sample of tumor tissue, mg	Weight of dried sample, mg (% from crude weight)	Concentration of Gd in dried sample, ppm (ng/mg)	Gd amount in tumour (in dried sample), ng	Concentration of Gd in tumour (recalculation on crude weight), ppm	Time between MRI and operation, days
1	1088	392 (36.03)	0.0259 ± 0.0006	10.1528	0.0093	6
2	971	169 (17.40)	1.37 ± 0.23	231.53	0.2384	6.5
3	2075	364 (17.54)	0.174 ± 0.035	63.336	0.0305	9
4	348	40 (11.49)	0.366 ± 0.140	14.64	0.0421	13
5	1176	157 (13.35)	0.387 ± 0.070	60.759	0.0517	189
Control without gadolinium						
6	1864	287 (15.40)	Below detection limit	-	-	5
7	660	111 (16.82)	Below detection limit	-	-	13

IV. Discussion

The obtained data demonstrate that after single intravenous injection of Magnevist the trace amount of gadolinium are retained in various concentrations in the brain tumours. It is possible to assume that gadolinium in tumours is present in bound form as it is found out in the range from 5 to 189 days after injection. Our obtained data agree with data [8,10] according to which accumulation of gadolinium in various parts of brain remains constant during the long life time. This effect is necessary to take in consideration for precise dosimetry calculations of absorbed dose in Gd-NCT.

The nature of mechanism of gadolinium accumulation in health brain tissues and in brain tumours (in our case) is not studied yet completely. In whole, in the studies spent earlier it was not found out any

phenomena of Magnevist metabolism [22]. But it is impossible to exclude completely the probability that detectable gadolinium accumulates due to appearance of free gadolinium because of biodegradation of chelate compounds of gadolinium. Besides there is probability of partial dissociation of chelate compounds of gadolinium in vivo and release of free gadolinium due to transmetallation [23]. In case of Magnevist the biodegradation or dissociation is prevented by addition of excess quantity of free ligand, therefore appearance of considerable quantity of free gadolinium as whole is excluded. Nevertheless, enough insignificant biodegradation or dissociation of preparation in order to released gadolinium could be captured and bound by brain tumour tissues.

At present time the clinical importance of revealed effect of accumulation of gadolinium in brain tumours after intravenous introduction of pharmacological chelate compounds of gadolinium is not clear enough. In 2006 the causal relationship of introduction of gadolinium and development nephrogenic systemic fibrosis in patients with pre-existing renal dysfunction [24] has been found out and proved. In the subsequent studies it has been proved that renal diseases are the cause of accumulation of gadolinium in skin of patients with nephrogenic systemic fibrosis [25]. This obtained data has caused questions on stability of gadolinium-based contrast agents (GBCAs) in vivo and their disposition to transmetallation (exchange of metal gadolinium with endogenous cation). However, during next several years the nephrogenic systemic fibrosis has been actually eradicated by reasonable use of GBCAs in patients with reduced renal function that has increased trust to safety of use GBCA in patients with maintained renal function [26-28].

Recently there was revealed indirect proof which assumes that gadolinium deposition can occur in patients with normal nephritic function. A few studies has shown progressive increases in T1-weighted MR signal in various structures of the central nervous system (CNS) after repeated administration of gadolinium [8,9].

As free gadolinium is toxic, so the establishment of fact of gadolinium accumulation in brain tumours can appear significant for interpretation of various unexpected clinical effects in the future.

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