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Gadolinium deposition in tissue following multiple contrast-enhanced MRI examinations

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Abstract: Gadolinium-based contrast agents (GBCAs) were considered extremely safe since their introduction for clinically used in 1988. However, in 2006, nephrogenic systemic fibrosis (NSF) was reported in patients with end-stage renal failure who were exposed to some GBCAs. In 2014, gadolinium deposition was found to occur in the brain tissues of patients exposed to multiple GBCA studies.

This project aimed to review currently published studies regarding gadolinium accumulation in tissues after repeated GBCA administrations to identify and summarize the recent findings for this issue. Six scientific databases were electronically searched for relevant studies between 2009 and July 2016. The reference lists were also checked and tracked to find related articles. Studies were evaluated for relevance either by scanning their title and abstracts or reading the full text.

The primary search yielded 1765 papers, which were then narrowed down to 14 studies that fulfilled the inclusion criteria. Two more studies were found by manually searching the reference lists. Of these, three studies assessed gadolinium retention in the brain tissues on animal models, while the remaining 13 were human research studies.

Keywords: Gadolinium deposition, Multiple GBCAs, Dentate nucleus, Globus pallidus.

Introduction

Since the initial approval to use gadolinium-based contrast agents (GBCAs) by the competent authorities, around 450 million doses of GBCAs have been administered around the world [(1)]. Compared with many other pharmaceuticals (i.e. iodinated contrast agents), GBCA has been extremely favorable and considered safe due to its small rates of adversative side effects [(2)]. There is an association between using GBCA in patients suffering severe renal function and developing infrequent condition nephrogenic systemic fibrosis (NSF) where contractures in muscles, predominately skin or fibrotic changes may occur [(3)]. Fortunately, the rapid development in the clinical practices of using GBCAs in renally impaired patients has fundamentally eliminated such clinical entity.

For a period of time, it had been widely thought that the ions of gadolinium remain chelated following GBCA intravenous administration; this was rapidly defeated. However, scientifically proven evidence has shown that the gadolinium traces remain in the brain, bones and other body organs in patients having a normal renal function [(4)]. The tissue retention extent tends to be associated with the cumulative

dosage. All linear and macrocyclic agents retain tissues of gadolinium where some of the existing data/studies suggest intraclass variability in such retention [5]. However, the relationship between the exposure and retention of GBCA and their symptoms are still unclear due to the symptoms inconsistencies related to GBCA administration and dose threshold i.e. timing and location [6].

There are 9 of GBCAs that have been regulatory approved in the United States of America where each of them has its unique physical and chemical properties as shown in Table (1). However, linear GBCAs types have been recently removed from the European market because of the rising concerns about gadolinium retention [7]. This difference is due to the difference in the country's regulatory approach to using GBCAs. Besides, it could be due to the lack of scientific research on the adverse effects of those agents especially their bio distribution and their long-term retention in tissues. Consequently, conducting research studies on the safety of GBCAs agents to highlight their side effects is indispensable for the medical service providers and patients who need to undergo GBCA.

Table (1) GBCAs' Physical and Chemical

Chemical Name	Structure	Ionicity	Protein Binding	*K*obs (sec^{-1}); T1/2	Log *K*therm	Log *K*cond	Elimination Half-Life (min)	Injected Dose Eliminated within 24 Hours (%)
Gadodiamide	Linear	Nonionic	No	12.7; < 5 sec	16.9	14.9	77.8 ± 16	95.4 ± 5.5
Gadoversetamide*	Linear	Nonionic	No	8.6; < 1 sec	16.6	15.0	NA	NA
Gadopentetate dimeglumine	Linear	Ionic	No	0.58; < 5 sec	22.5	18.4	96 ± 7.8	91 ± 13
Gadoxetate dimeglumine	Linear	Ionic	Yes	0.16; < 4 sec	23.5	18.7	54.6–57	Amount remaining was too small to be detected
Gadobenate dimeglumine	Linear	Ionic	Yes	0.41; < 5 sec to 121 ± 36	22.6	18.4	70 ± 16	80–98
Gadofosveset trisodium†	Linear	Ionic	Yes	2.9×10^{-2}; 24 sec	22.1	18.9	NA	NA
Gadoteridol	Macrocyclic	Nonionic	No	2.6×10^{-4}; 3.9 hr	23.8	17.1	94.2 ± 4.8	94.4 ± 4.8
Gadobutrol	Macrocyclic	Nonionic	No	2.8×10^{-5}; 43 hr	21.8	14.7	108 (72–393)	> 90
Gadoterate meglumine	Macrocyclic	Ionic	No	$2–8 \times 10^{-6}$; 338 hr	25.6	19.3	84 ± 12 (F), 72.9 ±17.0 (M)	120 ±42 (F), 84.4 ± 9.7 (M)

Source: Mcdonald et al. [8]

Research objectives

The aim of the current research is to review some of the recent studies about gadolinium deposition in tissues following multiple administrations of GBCA to explore its side effects and impact on the patient.

Review of Included Studies

In this section, the researcher describes studies included in this research.

Animal research

Robert et al. [9] showed that the repeated administrations of the linear GBCA gadodiamide to healthy rats are associated with progressive and persistent T1 signal hyperintensity in the deep cerebellar nuclei (DCN), with Gd deposition in the cerebellum in contrast with the macrocyclic GBCA gadoterate meglumine for which no effect was observed. Jost et al. [10] evaluated, in rats, T1-weighted signal intensity in the deep cerebellar nuclei (CN) and globus pallidus (GP) up to 24 days after repeated administration of linear and macrocyclic gadolinium-based contrast agents (GBCAs) using homologous imaging and evaluation methods. They found increased signal intensity in the CN was found up to 24 days after multiple, extended doses of linear GBCAs. Robert et al. [11] evaluated Gd retention in the DCN of linear gadolinium-based contrast agents (GBCAs) compared with a macrocyclic contrast agent. The study revealed that repeated administrations of the linear GBCAs gadodiamide, gadobenate dimeglumine, and gadopentetate dimeglumine to healthy rats were associated with progressive and significant T1 signal hyperintensity in the DCN, along with Gd deposition in the cerebellum. This is in contrast with the macrocyclic GBCA gadoterate meglumine for which no effect was observed. Bussi et al. [12] explored the impact of single and cumulative doses of MultiHance on toxicity, pharmacokinetics, tissue gadolinium presence, behavior and neurological function in juvenile rats. Gadolinium presence was variable across tissues and decreased during the 60-day treatment-free period. The highest levels were noted in the femur and the lowest levels in the brain. Gadolinium presence in juvenile rat brain following single or repeated MultiHance administrations was minimal and non-impactful. Finally, Boyken et al. [13] determined the gadolinium (Gd) concentration in different brain areas in a pig cohort that received repeated administration of Gd-based contrast agents (GBCAs) at standard doses over several years, comparable with a clinical setting. The deduced that multiple exposures to macrocyclic gadobutrol are not associated with Gd deposition in brain tissue of healthy pigs.

Human research

Kanda et al. [14] revealed that High SI in the dentate nucleus and globus pallidus on unenhanced T1-weighted images may be a consequence of multiple previous gadolinium-based contrast material

administrations. Errante et al. [15] found that the increase in the unenhanced T1 signal intensity has a linear relationship with the eMRIn in patients with MS and BM. Ramalho et al. [16] proved that gadolinium deposition occurs in the human brain after multiple gadolinium contrast administrations, despite an intact blood-brain barrier and normal renal function. Weberling et al. [17] found an increase in SI in the DN after serial injections of gadobenate dimeglumine. Quattrocchi et al. [18] found that the prolonged exposure of the capillary interface to dechelated gadolinium may contribute to the passage of the blood-brain barrier. Ramalho et al. [19] found an increased T1 signal change over time in patients who underwent gadobenate dimeglumine and had received prior gadodiamide compared to those without known exposure to previous gadodiamide. Adin et al. [20] showed that the repeated performance of gadolinium-enhanced studies likely contributes to a long-standing hyperintense appearance of dentate nuclei on precontrast T1-weighted-MR images. Kanda et al. [21] concluded that hyperintensity in the DN on unenhanced T1-weighted MR images is associated with previous administration of linear GBCA, while the previous administration of macrocyclic GBCAs showed no such association. Radbruch et al. [22] indicated that an SI increase in the DN and GP on T1-weighted images is caused by serial application of the linear GBCA gadopentetate dimeglumine but not by the macrocyclic GBCA gadoterate meglumine. In Cao et al. [23], unenhanced T1 signal hyperintensity was observed in the dentate nucleus after multiple administrations of gadopentetate dimeglumine, a linear ionic agent, but not after multiple administrations of gadobutrol, a macrocyclic GBCA. McDonald et al. [24] found that intravenous GBCA exposure is associated with neuronal tissue deposition in the setting of relatively normal renal function. Murata et al. [25] showed that the gadolinium deposition in the normal brain and bone tissue occurs with macrocyclic and linear protein interacting agents in patients with normal renal function. Finally, Stojanov et al. [26] found that patients with RRMS, SI within the dentate nucleus and globus pallidus increased on unenhanced T1-weighted images after multiple gadobutrol injections. Administration of the same total amount of gadobutrol over a shorter period caused greater SI increase.

Method and Procedures

The PubMed, Science Direct, ProQuest, Leeds library, Medline and Google Scholar databases were searched electronically for relevant studies that were published between 2009 and December 2018. Studies since 2009 were screened because some articles published before 2014 have reported hyperintensity in brain tissue on unenhanced T1-weighted images. The search terms used to find relevant articles are summarised in Table (2). The same search strategies were used for all the mentioned databases. The reference lists of the pertinent retrieved articles were manually tracked to identify additional relevant articles. The search process was completed on December 31, 2018.

Table (2) The search terms used to find relevant articles

Search Terms
Gadolinium MRI
AND
Deposit* OR retention* OR accumulated*
AND
Brain OR intracranial OR tissue.

The primary search process using the keywords mentioned above resulted in 3297 articles. After removing duplicates, 2985 papers remained. Of these, 2790 articles were deemed irrelevant by scanning the title and were excluded. An additional 154 papers were excluded by reading their abstract, which left 41 papers. A total of 22 of these articles were excluded after applying the previously mentioned exclusion criteria: 17 articles were reviews, six papers were commentary letters, and four were case reports. Of the remaining 27 studies, ten were excluded by reading the full text. These studies assessed hyperintensity in the DN on unenhanced T1W images due to several factors such as radiation therapy or progression of the existing disease but did not evaluate the impact of repeated GBCA administrations on unenhanced T1W SI. The reference lists of the relevant articles were manually searched, and two related articles (Adin et al., 2015; Weberling et al., 2015) were retrieved, increasing the number of relevant studies to 19.

The 19 included studies that fulfilled the inclusion criteria were initially classified based on study characteristics into animal research and human research. Five prospective studies (Robert et al., 2015; Jost et al., 2016; Robert et al., 2016, Bussi et al., 2017 and Boyken, et al., 2018) used animal models and compared the effect of multiple administrations of both macrocyclic and linear GBCAs on unenhanced T1W SI in deep cerebellar nuclei (DCN) involving the DN. The remaining 14 studies involved human patients.

The human studies were further divided into subgroups based on the type of GBCAs used and the study objectives. Seven studies (Kanda et al [(14)]; Errante et al. [(15)]; Ramalho et al [(16)]; Weberling et al. [(17)]; Quattrocchi et al [(18)]; Adin et al. [(20)]; Ramalho et al. [(19)] assessed the correlation between previous multiple linear GBCA administrations and gadolinium retention that caused hyperintense DN on unenhanced T1W images. McDonald et al. [(24)], Murata et al. [(25)], Bussi, et al. [(17)] and Lim et al. [(27)] examined the association between repeated GBCA administration and neural tissue deposition in deceased patients. Another three studies (Kanda et al. [(21)]; Radbruch et al. [(22)]; Cao et al. [(23)] compared the effects of previous multiple administrations of both macrocyclic and linear GBCAs on unenhanced T1W SI of the DN and GP. Stojanov et al. [(26)] evaluated the association between cumulative doses of macrocyclic GBCA, gadobutrol, and SI in both DN and GP on unenhanced T1W images. A summary of these studies is shown in Table (3).

Research Design and Sample

The following criteria were utilized to determine studies for the current review.

Inclusion criteria

- Prospective or retrospective studies that were conducted either on human patients or animal models to evaluate gadolinium deposition in tissue.
- Studies that assessed the correlation between increased SI in brain tissue on unenhanced T1W images and repeated administrations of different classes of GBCAs.
- Studies performed to evaluate high SI in the brain tissue of patients with known diseases who received repeated administrations of GBCAs.

Table (3) lists the included studies.

Exclusion criteria

- Studies that did not evaluate gadolinium deposition in tissue following repeated GBCA administrations.
- Literature reviews and commentaries.
- Systematic Reviews
- Case reports.
- Papers that reported general information about CE-MRI or chemical properties of GBCAs.

Data extraction

Data extracted from the relevant studies included the aim, study characteristics, type of GBCAs used in the study, interpretation of the results, and outcome of the studies.

Table (3) Summary of included studies

Study characteristics							
Study	Study type	Population number	Female	Male	Mean age Years	Type of GBCAs	Methods of gadolinium deposition assessment
Animal studies							
Robert et al. [9]	Prospective	21 rats	21	0	--	Linear and macrocyclic	—DCN/ cerebellar cortex SI ratio —CP-MS to measure Gd concentration in brain tissue sample
Jost et al. [10]	Prospective	60 rats	0	60	--	Linear and macrocyclic	—DCN/pons SI ratio —CSF spaces
Robert et al. [11]	Prospective	40 rats	40	0	--	Linear and macrocyclic	—DCN/ cerebellar cortex SI ratio —ICP-MS for tissue analysis, R1 mapping
Bussi et al., [12]	Prospective	486 rats	243	243	--	Linear and macrocyclic	—ICP-MS to measure tissue samples of the brain (cerebellum, cerebral cortex, subcortical brain).
Boyken et al., [13]	Prospective	13 pigs	0	13	--	Linear but Not Macrocyclic	—ICP-MS to analyze tissues from multiple brain areas including cerebellar and cerebral deep nuclei, cerebellar and cerebral cortex, and pons.
Human studies							
Kanda et al. [14]	Retrospective	19 16 (control)	9 10	10 6	67.7 73.5	Linear ionic	—DN to pons and GP to thalamus SI ratios and Random coefficient model to assess SI
Errante et al. [15]	Retrospective	38 MS** 37 BM**	27 18	11 19	47 62	Linear non-ionic	—DN to pons SI ratio and relative change in the SI
Ramalho et al. [16]	Retrospective	23 (linear non-ionic) 46 (linear ionic)	19 24	4 22	51.2 60.2	Linear ionic and non-ionic	—DN/middle cerebellar peduncle (MCP) and GP/thalamus SI ratio and relative change in the SI were measured.
Weberling et al. [17]	Retrospective	50	22	28	60.4	Linear ionic	—DN to CSF and DN to pons SI ratio were measured
Quattrocchi et al. [18]	Retrospective	46	40	6	66.5	Linear non-ionic	—Calculation of DN to pons SI ratio

Study characteristics							
Study	Study type	Population number	Female	Male	Mean age Years	Type of GBCAs	Methods of gadolinium deposition assessment
Ramalho et al. [19]	Retrospective	18 (ionic & non-ionic) 44 (ionic)	16 23	2 21	56.5 60.4	Linear non-ionic	—DN to MCP
Adin et al. [20]	Retrospective	184	83	101	43.3	Linear	—DN/MCP SI ratio —Assessed gadolinium retention among other confounders
Kanda et al. [21]	Retrospective	127	69	58	60.4	Linear and macrocyclic	—DN/cerebellum SI ratios —Differences in SI between last and first GBCAs CE-MRI scan
Radbruch et al. [22]	Retrospective	50 (macrocyclic) 50 (linear)	23 20	27 30	49.9 46.8	Linear and macrocyclic	—DN/pons and GP/ thalamus mean SI ratios —Regression analysis
Cao et al. [23]	Retrospective	25 (macrocyclic) 25 (linear)	10 10	15 15	54 53	Linear and macrocyclic	—DCP SI ratio before and after GBCA injections.
McDonald et al. [24]	Retrospective (Autopsy)	13 + (10 control)	--	--	--	Linear	—Neuronal tissue samples were taken from the brain and analyzed with ICP-MS
Murata et al. [25]	Retrospective (Autopsy)	9 + (9 control)	8	10	56.61	Linear protein binding GBCAs and macrocyclic	—ICP-MS for gadolinium retention in tissue samples from bone, skin, and brain.
Stojanov et al. [26]	Retrospective	58	37	21	42.38	Macrocyclic	—DN/pons & GP/Thalamus SI ratios —Correlation between No. of GBCA injections and high SI.
Lim et al., [27]	Retrospective	44	15	29	54.3	Macrocyclic	Evaluate the possibility of accelerated gadolinium accumulation in irradiated brain parenchyma

Notes: (*) Represents only the number of subjects included in the study who fulfilled the inclusion criteria. (MS**) patients with multiple sclerosis, (BM**) patients with brain metastasis. Gd= gadolinium, ICP-MS=inductively coupled plasma mass spectrometry.

Results and Discussion

The modern day MRI scanning can primarily be done in two methods, firstly without using contrast agents and the second, using contrast agents. MRI contrast involves using some extra component such as a dye for the scan, thus enabling better imaging in the process [28]. The most commonly employed diagnostic agents or dyes make use of Gadolinium, which is a "rare earth metal" that acts as a "contrast enhancer," thus making the areas of the body underscan "more visible" [29]. MRI, as a “diagnostic imaging modality,” renders several benefits, as it is “non-invasive, delivers no radiation burden” and has excellent “spatial resolution” [31]. This coupled with the increased visibility that contrast agents offer, MRI scans help in detecting what the exact problem a patient is suffering from and therefore enable appropriate diagnosis. In clinical imaging, basically the hydrogen atoms constituting water present in tissues are observed, thus the use of contrast agents “catalytically shortens the relaxation times of bulk water protons,” making tissues visible more accurately [31].

Some of the Gadolinium-based contrast agents used in MRI scans are "gadopentetate dimeglumine (Magnevist), gadoterate meglumine (Dotarem), gadoteridol (ProHance) gadodiamide (Omniscan), gadobenate dimeglumine (MultiHance), gadobutrol (Gadovist) and gadoversetamide (OptiMARK), Vasovist (gadofosveset)" etc [31]. While some of these agents are ionic in nature, some are non-ionic and based on their thermodynamic property and kinetic stability different agents are used in different MRI scans. While the contrast agents seem highly relevant in making body tissues more visible, due to the chemical properties of the substances used in dyeing, people often seem to suffer from various side effects. Mild reactions to contrast agents include "nausea, headaches, dizziness, hives, rash, chills, pallor" etc, whereas moderate reactions include "tachycardia/ bradycardia, bronchospasm, wheezing, dyspnea, pronounced cutaneous reaction, laryngeal edema, pulmonary edema, hypertension" and so on. However, sometimes side effects can be highly wide-ranging and even cause life-threatening issues such as "cardiopulmonary arrest, clinically manifest arrhythmias, profound hypotension, unresponsiveness and convulsions" [32].

Adding to the issue of side effects caused by contrast based MRI scans are the high costs incurred in the process. The use of contrast agents and dyes undoubtedly leads to increased cost because gadolinium, as mentioned before, is a rarely found chemical substance. Furthermore, various alternatives can be used to perform scans instead of MRI, such as computed tomography (CT) scans, ultrasound, x-rays, digital subtraction angiography etc. In the case of scans for the brain, CT venography is a powerful tool, which facilitates the assessment of sinus thrombosis with cost-effectiveness [33].

Gadolinium as already discussed in the studies included in this paper. It is used as a contrast medium that makes certain tissues more vividly visible on an MRI scan. This agent is known to improve diagnostic accuracy in certain conditions such as inflammation as well as infectious diseases affecting bones, brain, spine and soft tissues. The contrast medium comprises of gadolinium ion bonded by a carrier molecule called cheating agent. The studies have shown that certain reported reactions that rarely occur are a brief headache, dizziness a few minutes following the injection. However, patients with reduced kidney function or kidney failure and hepatorenal syndrome should not be administered by this agent. Some patients were also found to be suffering from nephrogenic systemic fibrosis (NSF), a disease resulting in skin thickening and tightening as well as internal organ damage, occurring in people previously suffering from kidney abnormalities [(34)]. People with normal kidney function are insusceptible to this disease.

Although the included studies showed an association between repeated administration of GBCAs and gadolinium retention in the brain tissue, the mechanism of gadolinium retention is still not clear. None of the included studies investigated whether the retained gadolinium in tissue remained chelated or in a free ion status. Some researchers have speculated on the form of retained gadolinium. Quattrocchi et al. [(18)] suggested that chelated GBCA could not pass through the intact blood-brain barrier, but it might dissociate at the DN capillary interface. However, McDonald et al. [(24)] demonstrated that gadolinium from injected GBCA could pass through the intact blood-brain barrier because the authors noted multiple punctate foci of gadolinium within the neural capillary endothelium, which was an indicator of the sound barrier. To dates, there have been no reports of clear mechanism or specific clinical significances of gadolinium deposition in tissues in patients with normal renal function.

The main limitation of the current review was that some of the included studies had a small sample size and were not excluded. In addition, the quality of the included studies was not assessed with a formal checklist, because the review aimed to identify evidence regarding gadolinium deposition in tissue.

Conclusion

In conclusion, this review revealed that there is some evidence to conclude that gadolinium retention in the tissue of patients with normal renal function is associated with multiple injections of less stable GBCAs. However, this evidence is still under investigation and unconfirmed by the US FDA. The reviewed studies' results showed significant increases in the SI of the DN and GP on unenhanced T1W images after multiple administrations of linear GBCAs. Gadolinium retention in neuronal tissues is higher after successive administrations of linear non-ionic GBCAs than linear ionic GBCAs. Although most of the included studies reported no change in the SI of the DN and GP after multiple administrations of macrocyclic GBCAs, two studies reported an increase in the T1W SI in the DN following those administrations. Notably, these findings

are unconfirmed due to methodological limitations, involving a small sample size. Gadolinium may accumulate in the bone, brain, and skin of patients with normal renal function; however, further large-scale studies are required to verify these findings. The mechanism of gadolinium deposition and whether the detected gadolinium in tissue remains chelated or as free ions remain unclear. Further studies are required to determine the specific type of GBCAs that can cause gadolinium retention and to identify the mechanism and clinical significance of this concern. Finally, throughout the reviewed studies, the clinical implications of gadolinium in tissue following multiple contrast-enhanced MRI examinations remain unclear and require further investigations. Besides, researchers and medical cadres are recommended to conduct more studies on the human being in order to find clear cut results concerning the retained gadolinium in tissue following multiple contrast-enhanced MRI examinations.

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ترسب الجادولينيوم في الأنسجة بعد الخضوع المتعدد للتصوير بتقنية الرنين المغناطيسي المحسنة بالصبغة

الملخص: تعتبر عوامل التباين القائمة على الجادوليوم (GBCAs) آمنة للغاية منذ إدخالها للاستخدام في مجال التصوير في عام 1988. وعلى الرغم من ذلك، في العام 2006، تم اكتشاف أضراراً صحية للجهاز على المرضى الذين يعانون من الفشل الكلوي بعد تعرضهم لعدة مرات من التصوير. وفي العام 2004، تم اكتشاف بعض من ترسبات الجادوليوم في أنسجة دماغ بعض المرضى الذين تعرضوا للتصوير عدة مرات.

في ضوء ذلك، هدفت الدراسة الحالية إلى استعراض ومراجعة بعض الدراسات المنشورة حاليًا فيما يتعلق بتراكم الجادولينيوم في الأنسجة بعد التعرض للتصوير عدة مرات، وذلك لتحديد وتلخيص النتائج الحديثة لهذه المسألة. ولتحقيق ذلك، تم البحث في ستة قواعد بيانات علمية إلكترونياً للدراسات ذات الصلة بين الأعوام 2009 وديسمبر 2019 حيث تم فحص قواعد البيانات ومراجعتها وتتبعها للعثور على المقالات ذات الصلة. تم تقييم الدراسات لملاءمتها عن طريق مسح عناوين وملخصات أو قراءة النص الكامل.

شمل البحث المبدئي 1765 بحثًا ، ومن ثم تم حصرها في 14 دراسة حققت معايير الاختيار. تم الحصول على اثنين من الدراسات عن طريق البحث يدويا في قوائم المراجع. من هذه ، قيمت ثلاث دراسات احتباس الجادولينيوم في أنسجة المخ على نماذج حيوانية، في حين أن الثلاثة المتبقية كانت دراسات بحثية على البشر.

الكلمات المفتاحية: ترسب الجادوليوم، التصوير المتعدد بالرنين المغناطيسي، النَّواةُ المُسَنَّنَة، الكُرَةُ الشَّاحِبَةُ الإِنْسِيَّة.