J Surg Med. 2019;3(8):629-630.
DOI: 10.28982/josam.602855

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Re: “Increased signal intensity in the unenhanced T1-weighted magnetic resonance in the brain after repeated administrations of a macrocyclic-ionic gadolinium-based contrast agent”

Re: “Makrosiklik-iyonik gadolinyum-bazlı kontrast ajan ile tekrarlanan uygulamalar ile T1 ağırlıklı kontrastsız manyetik rezonans görüntülemedeki sinyal intensite artışı”

Sébastien Ballet [1], Pierre Desché [1]

[1] **Guerbet, Roissy CDG Cedex, France**

ORCID ID of the author(s)
SB: 0000-0002-5184-4946
PD: 0000-0002-2389-0697

Keywords: Gadolinium retention, Brain MRI, T1 hypersignal

Anahtar kelimeler: Gadolinyum tutma, Beyin MRI, T1 hipersinyal

Dear Editor,

We have read with a great interest the paper by Kavak and Özdemir [1], recently published online in the Journal of Surgery and Medicine. In a total of 61 patients with lung cancer, with no brain metastasis, no history of radiation, no history of renal failure they reported an increase in signal intensity (SI) in unenhanced T1-weighted MRI in the brain following repeated administrations of gadoterate meglumine at the standard dose of 0.1 mmol/kg of body weight. The increase in SI was reported in several brain areas: dentate nucleus (DN), pons (P), globus pallidus (GP) and thalamus (T). As stated by the authors, the mean SI in DN, P, GP and T were divided by the mean values obtained from the cerebrospinal fluid (CSF) to standardize the SI measurements and an increase in the four respective ratios was reported as well. These results are conflicting with all the published data from well controlled studies showing no increase in signal intensity with macrocyclic agents [2]. Furthermore, several methodological aspects of that study do not match with the recently published recommendations [2].

First, although it is stated that a minimum of 3 injections and a maximum of 5 injections were given, the cumulative dose (mean and range) of gadoterate meglumine is not specified.

Second, the DN-to-pons ratio has not been assessed although this ratio has been used in most of the reported studies. The author did not justify why they did not choose pons as the reference region. Considering the pharmacokinetic profile of macrocyclic agents in the CSF compartment [3, 4, 5], CSF is not an appropriate reference region to standardize SI values from other cerebral regions. The reported ratio increases (DN/CSF, P/CSF, GP/CSF, T/CSF) could be due to specific variations from CSF signal intensity. In addition, since the ratio of the means is different from the mean of the individual ratios, the ratios should have been calculated for each individual instead of dividing, for each specific brain area, the mean SI by the mean SI in CSF. Last, but not least, the increase in SI value in pons, which is commonly recognized as reference region, strongly suggests an experimental bias favorizing a global increase in SI values in multiple brain regions beyond the DN and GP known as the specific brain regions for gadolinium deposition.

Third, there was no control group without gadolinium-based agents injection. In absence of control group, the impact of CSF SI on SI ratio values cannot be evaluated and increases in SI values cannot be confirmed.

Fourth, DN, P, GP, and T SI changes were reported between first and last unenhanced MRI. Additional time points, which were available in this study, since correlation between ratio values and number of MRI was tested, should have been shown for a robust conclusion.

Corresponding author / Sorumlu yazar:
Sébastien Ballet
Address / Adres: Guerbet, BP57400, 95943
Roissy CDG Cedex, France
e-Mail: sebastien.ballet@guerbet.com

Ethics Committee Approval: The letter is not a study with human participants. There are no experiments on animals. This letter does not contain any studies on human participants or animals performed by the author. There is no identifying information of participants.
Etik Kurul Onayı: Bu mektup, insan katılımcılarla yapılan bir çalışma değildir. Hayvanlar üzerinde deney yoktur. Bu mektupta, insan katılımcıları veya yazar tarafından gerçekleştirilen hayvanlar üzerinde yapılan hiçbir çalışma yoktur. Katılımcıların tanımlayıcı bilgisi yoktur.

Conflict of Interest: No conflict of interest was declared by the authors. The authors of this letter are employees of Guerbet.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir. Bu mektubun yazarları Guerbet'in çalışanlarıdır.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 8/9/2019
Yayın Tarihi: 09.08.2019

How to cite / Atıf için: Ballet S, Desché P. Re: “Increased signal intensity in the unenhanced T1-weighted magnetic resonance in the brain after repeated administrations of a macrocyclic-ionic gadolinium-based contrast agent” J Surg Med. 2019;3(8):629-630.

Fifth, it is stated that “The number of examinations had a moderately positive correlation with DN/CSF ratio and a strongly positive correlation with the P/CSF ratio” which is not consistent with the correlation coefficient values reported in the Table 3, e.g. 0.490 and 0.577, respectively. Both values represent only moderate correlation. In the absence of individual data (which could have been reported in a graph) the conclusion is misleading.

Finally, the Stojanov [6] and Rossi-Espagnet [7] studies were reported without mentioning the respective associated controversies on these publications [8,9].

Taking into consideration these significant limitations, the authors might mitigate their conclusion emphasizing that further studies – with more robust approach - should be investigated to confirm these unexpected results.

References

1. Kavak RP, Özdemir M. Increased signal intensity in the unenhanced T1-weighted magnetic resonance in the brain after repeated administrations of a macrocyclic-ionic gadolinium-based contrast agent. J Surg Med. 2019;3(7):507-11.
2. Quattrocchi CC, Ramalho J, van der Molen AJ, Rovira À, Radbruch A et al. Standardized assessment of the signal intensity increase on unenhanced T1-weighted images in the brain: the European Gadolinium Retention Evaluation Consortium (GREC) Task Force position statement. Eur Radiol. 2019;29(8): 3959-67.
3. Berger F, Kubik-Huch RA, Niemann T, Schmid HR, Poetzsch M, Froehlich JM et al. Gadolinium distribution in cerebrospinal fluid after administration of a gadolinium-based MR contrast agent in humans. Radiology. 2018;288(2):703-9.
4. Nehra AK, McDonald RJ, Bluhm AM, Gunderson TM, Murray DL, Jannetto PJ et al. Accumulation of gadolinium in human cerebrospinal fluid after gadobutrol-enhanced MR imaging: a prospective observational cohort study. Radiology. 2018;288(3):416-23.
5. Ohashi T, Naganawa S, Ogawa E, Katagiri T, Kuno K. Signal intensity of the cerebrospinal fluid after intravenous administration of gadolinium-based contrast agents: strong contrast enhancement around the vein of Labbe. Magn Reson Med Sci. 2019;18(3):194-9.
6. Stojanov DA, Aracki-Trenkic A, Vojinovic S, Benedeto-Stojanov D, Ljubisavljevic S. Increasing signal intensity within the dentate nucleus and globus pallidus on unenhanced T1W magnetic resonance images in patients with relapsing-remitting multiple sclerosis: correlation with cumulative dose of a macrocyclic gadolinium-based contrast agent, gadobutrol. Eur Radiol. 2016;26(3):807-15.
7. Rossi Espagnet MC, Bernardi B, Pasquini L, Figà-Talamanca L, Tomà P, Napolitano A. Signal intensity at unenhanced T1-weighted magnetic resonance in the globus pallidus and dentate nucleus after serial administrations of a macrocyclic gadolinium-based contrast agent in children. Pediatr Radiol. 2017;47(10):1345-52.
8. Agris J, Pietsch H, Balzer T. What evidence is there that gadobutrol causes increasing signal intensity within the dentate nucleus and globus pallidus on unenhanced T1w MRI in patients with RRMS? Eur Radiol. 2016;26(3):816-7.
9. Lancelot E, Raynaud J-S, Desché P. Lack of evidence of a relationship between magnetic resonance signal intensity changes in the globus pallidus and dentate nucleus, and repeated administrations of gadoterate meglumine in children. Pediatri Radiol. 2017;47(12):1692-3.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine