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ORIGINAL ARTICLE

Does Gadopentetate Dimeglumine Induce Gadolinium Accumulation in the Brains of Children?

Gadopentetate Dimeglumine, Çocukların Beyinlerinde Gadolinyum Birikimine Neden Olur Mu?

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ABSTRACT

Aim: To determine T1-weighted (T1W) signal intensity (SI) differences in the dentate nucleus (DN) and globus pallidus (GP) following contrast enhanced magnetic resonance imaging (MRI) with multiple gadopentetate dimeglumine administrations in a group of pediatric patients.
Methods and materials: This retrospective study included children with at least two enhanced brain MRIs. All patients received gadopentetate dimeglumine intravenously (0.1 mmol/kg). SI measurements were done by drawing five region of interests (ROI) on dentate nuclei (DN) and globus pallidi (GP) bilaterally and cerebro-spinal fluid (CSF) in unenhanced T1W images. Paired samples t-test was used for comparison of SI. Pearson correlation was calculated for the correlation between the SI and the number of gadolinium administrations.
Results: A total of 31 children (age range: 3-17 years; mean 10.6±4.3 years) were included. There was no significant difference between the first and the third MRI scans by means of the T1 SI ratios: right and left DN/CSF, right and left GP/CSF (P =0.543, P =0.599, P =0.803, P =0.730, respectively). 18 patients received more than two gadopentetate dimeglumine, the mean number of administrations was 5±3. A significant difference was detected between first and last MRI scans; right and left DN/CSF, right and left GP/CSF (P=0.004, P=0.008, P=0.001, P=0.014 respectively). Correlation between the number of gadopentetate dimeglumine administrations and the SI for right and left DN/CSF, right and left GP/CSF (r=0.13, r=0.13, r=0.09 and r=0.12, respectively) was poor (P=0.189, P=0.205, P=0.472 and P=0.095, respectively).
Conclusion: There was no significant T1 SI increase for children with at least two gadopentetate dimeglumine administrations but after multiple administrations, significant T1 SI increase was found in this series.

Key words: Brain MRI; contrast agent; gadolinium accumulation; linear

ÖZ

Amaç: Kontrastlı manyetik rezonans görüntüleme (MRG) için tekrarlayan gadopentetate dimeglumine uygulanan pediyatrik hastalarda dentat çekirdek (DÇ) ve globus pallidus'ta (GP) ağırlıklı (T1A) sinyal yoğunluğu (SI) farklılıklarını belirlemek.
Gereç ve Yöntem: Bu retrospektif çalışmaya, kontrast madde olarak en az iki kez intravenöz olarak gadopentetate dimeglumine uygulanan (0.1 mmol/kg) ve kontrastlı beyin MRG yapılan çocuk hastalar dahil edildi. SI ölçümleri, kontrastsız T1A görüntülerinde bilateral dentat çekirdekler (DN) ve globus pallidi (GP) ve beyin omurilik sıvısı (BOS) üzerine beş ROI alanı çizilerek yapıldı. SI karşılaştırması için Student t testi kullanıldı. SI ile gadolinyum uygulama sayısı arasındaki korelasyonu değerlendirmek için Pearson korelasyonu hesaplandı.
Bulgular: Toplam 31 çocuk (yaş aralığı: 3-17 yıl; ortalama 10.6±4.3 yıl) çalışmaya dahil edildi. T1 SI oranları açısından birinci ve üçüncü MRG taramaları arasında anlamlı bir fark yoktu: sağ ve sol DN/CSF, sağ ve sol GP/CSF (P =0.543, P =0.599, P =0.803, P =0.730 , sırasıyla). İkiden fazla gadopentetate dimeglumine uygulanan 18 hasta mevcuttu ve ortalama uygulama sayısı 5±3'tü. İlk ve son MRG taramaları arasında T1 S1 oranları arçısından anlamlı bir fark saptandı; sağ ve sol DN/CSF, sağ ve sol GP/CSF (sırasıyla P=0.004, P=0.008, P=0.001, P=0.014). Gadopentetate dimeglumine uygulamasının sayısı ile sağ ve sol DN/CSF, sağ ve sol GP/CSF (sırasıyla r=0.13, r=0.13, r=0.09 ve r=0.12) SI değerleri arasındaki korelasyon zayıftı (sırasıyla P=0.189, P=0.205, P=0.472 ve P=0.095).
Sonuç: Bu seride iki kez gadopentetate dimeglumine uygulaması sonrası DN ve GP 'de anlamlı T1 SI artışı olmazken çoklu uygulama sonrası anlamlı T1 SI artışı bulundu.

Anahtar kelimeler: Beyin MRG, kontrast madde, gadolinyum birikimi, lineer

Introduction

For many years gadolinium-based contrast agents (GBCAs) are used as an essential component of neuroimaging and they have been accepted safe. It has firstly been reported by Kanda et al. (1) that (GBCA) administration for magnetic resonance imaging (MRI) can result in gadolinium (Gd) deposition in the brain and is associated with increased intrinsic signal intensity (SI) on T1-weighted (T1W) images after repeated administrations. Another study performed on human autopsies suggested Gd accumulation in all areas of brain but mostly at DN and GP. (2) Also, McDonald et al. (3) described a dose-dependent relationship with the number of repeated GBCA administration.

Up to date, most studies investigating GBCA retention in the brain have been performed in adults and several studies have shown SI changes in the brains of children exposed to repeated doses of GBCAs. (4-8) Although the long-term effects and the clinical significance of retained gadolinium are uncertain, more emphasis should be placed on GBCA accumulation in children's brains since they are more susceptible to toxins and

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expected lifetime exposure dose is greater than adults. (9,10)

There are two different kinds of GBCAs as linear and macrocyclic molecules. All GBCAs consist of a Gd ion and its carrier molecule called chelating agent. Its toxicity depends on the Gd3+ ion's dissociation from chelating agent. Macrocyclic and linear agent deposition in the brain is still unclear. In some studies, T1 signal changes in the DN and GP were demonstrated after the administration of linear GBCA. (11) However, there are controversial studies in the literature about macrocyclic agents. Some studies suggesting that repeated macrocyclic gadolinium-based contrast agent administration did not cause significant signal intensity increase in the DN and GP; but some studies suggests that gadolinium deposition occurs with some types of macrocyclic agent administrations (12).

In this study, we aimed to determine T1-weighted (T1W) signal intensity (SI) differences in the dentate nucleus (DN) and globus pallidus (GP) following contrast enhanced magnetic resonance imaging (MRI) with at least two gadopentetate dimeglumine administrations in pediatric patients.

Methods and Materials

Patient Selection

The requirement for informed consent was waived before the contrast-enhanced MRI. A search in the picture archiving and communication system of our department identified 91 consecutive pediatric patients who underwent contrast-enhanced brain MRI between the years of 2011 and 2021.

The most widely used contrast agent for MR imaging at our institution was gadopentetate dimeglumine (Magnevist; Bayer Health Care Pharmaceuticals, Wayne, New Jersey), though gadodiamide (Omniscan; GE Healthcare, Piscataway, New Jersey) and gadobenate dimeglumine (MultiHance; Bracco Diagnostics) were also used. In order to study in a homogenous group of patients we limited the assessment to one agent, and we included the patients who had enhanced brain MRI with at least two gadopentetate dimeglumine administrations regarding to the information recorded by the MR imaging technologist at the time of the scan.

The exclusion criteria were as the following: (1) mass at the SI measurement areas (pontine glioma, drop metastasis, cerebellar mass), (2) anatomical defects and ponto-cerebellar hypoplasia, (3) previous history of posterior fossa surgery, (5) history of brain radiation therapy (5) diagnosis of congenital metabolic disease, tuberosclerosis (4) renal dysfunction (glomerular filtration rate < 45 ml/min/1.73 m2), (5) brain MRIs with other linear GBCAs, (6) T1W images with inadequate quality and artifacts. Finally, 31 patients were enrolled in the study.

The T2-weighted and precontrast T1-weighted images of the brain MRIs in pediatric age group were retrospectively evaluated by two radiologists with an experience of 10 and 11 years in consensus. At 31 patients, non-enhanced T1W images of first and third scans after two times gadopentetate dimeglumine administration were evaluated. Among these patients, at 18 patients who had been administered gadopentetate dimeglumine multiple times, non-enhanced T1W images of first and last scans were evaluated.

MRI technique

All MR images were obtained by a 3T (Philips, Ingenia, Netherlands) with a standard head-coil. The routine enhanced brain MRI protocols varied based on clinical indication. The study protocol consisted of unenhanced T1W turbo spin-echo without fat suppression, T2W turbo spin-echo in axial planes. MR imaging parameters for T1W images were as follows: slice thickness, 1 mm; slice gap, 1.3 mm; repetition time, 9.5-10 msec; echo time, 450-460 msec; image matrix, 256 x 256 pixels; flip angle, 8°. MR imaging parameters for T2W images were as follows: slice thickness, 5 mm; slice gap, 1.5 mm; repetition time, 4050-5100 msec, echo time, 80-90 msec; image matrix, 256 x 256 pixels; flip angle, 150°.

All patients in the study group received at least two intravenous gadopentetate dimeglumine (0.1 mmol/kg) administrations (2 injections; n=13, 3 injections; n=9, 4 injections; n=3, 5 injections; n=3, 6 injections; n=1, 10 injections; n=1 and 12 injections; n=1). Gadopentate dimeglumine (Magnevist; Bayer Healthcare Pharmaceuticals, USA) was used as 0.1 mmol/kg with a flow rate of 2 mL/sec. The GBCA type and dose at each scan were recorded in our institution's PACS information system.

Image Analysis

T1 weighted images of the brain MRI screening were evaluated by two radiologists with an experience of 10 and 11 years in consensus. Two different anatomic locations were selected bilaterally as dentate nuclei (DN) and globus pallidus (GP) for the SI measurements. 10 mm2 of 5 regions of interests (ROIs) were drawn manually onto the each anatomic location on non-enhanced axial T1W images for each side of the brain by using T2W images as a reference. Another ROI was drawn onto the cerebrospinal fluid (CSF) at 4th ventricle and the measured SIs were divided by the SI of CSF for standardization and the ratios were noted for each subject. In order to determine the correlation between the number of gadopentetate dimeglumine administrations and the SI, the measurements on nonenhanced T1W images were repeated for the first, third and the last MRI scans and compared with each other.

Statistical analysis

Descriptive data are reported as mean ± standard deviation (SD) for continuous parametric variables. Paired samples t test was used for comparison of SI derived from first and third scans of all patients and first and the last scans of 18 patients who had multiple scans. Pearson correlation was calculated for the correlation between the SI and the number of gadolinium administrations.

IBM SPSS Statistics, version 21, for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

A P value of <0.05 was considered as statistically significant.

Results

The present cohort was comprised of a total of 31 children (age range: 3-17 years; mean 10.6±4.3 years). The diagnoses of children who underwent brain MRI were; glial tumors (n=15), demyelinating disease (n=1), epidermoid cyst (n=1), Langerhans cell histiocytosis (n=1), AVM (n=2), cavernoma (n=1), intracerebral hemorrhage (n=1), nonglial tumors (n=9).

Mean time interval between first and third MRI scans after two times GDBCA administrations were 7.8 ± 9.7 months (range: 1-48 months).

There was no significant difference between the first and the third MRI scans by means of the T1 SI ratios: right and left DN/CSF, right and left GP/CSF (P =0.543, P =0.599, P =0.803, P =0.730, respectively). 18 patients received more than two gadopentetate dimeglumine, the mean number of administrations was 5±3. Mean time interval between first and last MRI scans was 21±19.5 months (range: 1-73 months). A significant difference was detected; right and left DN/CSF, right and left GP/CSF (P=0.004, P=0.008, P=0.001, P=0.014 respectively).

The mean T1 signal intensities ratios measured at MRI scans and p values of comparison of SI derived from first and third/last MRI scans are summarized in Table 1.

Table 1. Locations, mean signal intensity ratios measured at MRI scans and p values of comparison of SI derived from first and third/ last MRI scans.

Location	Mean±SD signal intensities (SI)				
	1st scan	3rd scan	P value	Last scan	P value
R DN/CSF	5.1± 2.9	5.5±1.9	0.543	6.3±1.9	0.004
L DN/CSF	5.0± 2.6	5.4±1.9	0.599	6.2±1.8	0.008
R GP/CSF	5.4± 2.7	5.6±1.9	0.803	6.4±2	0.001
L GP/CSF	5.2± 2.6	5.4± 2	0.730	6.2±2.2	0.014

Hyperintensity in the DN after recurrent injections were visible on T1W images, as shown in Figure 1.

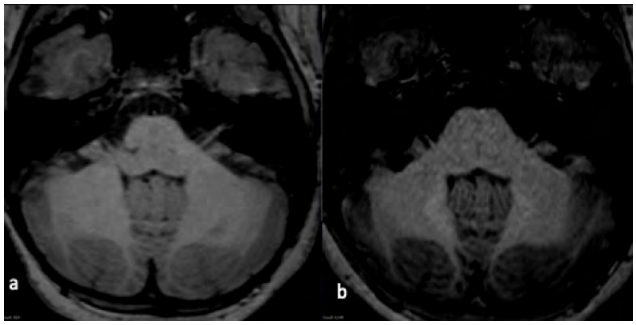

Figure 1. Axial T1 weighted images, first (a) and tenth (b) MR examinations in a 15-year-old girl with intracranial mass. Dentate nucleus T1 signal intensity shows marked increase after 10 gadopentetate dimeglumine injections.

Correlation between the number of gadopentetate dimeglumine administrations and the SI for right and left DN/CSF, right and left GP/CSF (r=0.13, r=0.13, r=0.09 and r=0.12, respectively) was poor (P=0.189, P=0.205, P=0.472 and P=0.095, respectively).

Discussion

The current study with pediatric age group demonstrated a significant SI increase in the DN and GP on unenhanced T1W images after repeated linear GBCA, gadopentetate dimeglumine administrations. In mostly previous studies patient cohorts consist of adult patients. There are only few studies focused on specific one contrast agent in pediatric patients. Roberts et al. reported SI increase in the DN and GP of children with repeated use of gadopentetate dimeglumine at least five times. (5) In their study, they also excluded the examinations performed with other linear contrast agents. Our findings are also consistent with previous published studies in pediatric patients that showed association between repeated administration of the linear GBCA gadopentetate dimeglumine and T1-weighted hyperintensity in the dentate nucleus. (5,6,11,13)

Towbin et al. demonstrated that T1 SI ratios significantly increased in globus pallidus, dentate nucleus and pulvinar with an increasing number of gadopentetate dimeglumine administrations in their study with 50 patients. (14) Also they reported that SI increase varied according to scanner vendor and MRI sequence type. In our study, since all MRI examinations were achieved with one device, we did not observe such a result.

In the current study, besides of first and last scans, SI at third scan of all patients after two gadopentetate dimeglumine injections was also measured and no significant increase was found. Also Mc Donald et al. reported that there must be at least 4 administration for gadolinium accumulation in the brain. (3) However, Miller et al. reported that gadopentetate dimeglumine accumulation at pediatric brain could be seen early at second or third MRI scan. (4) It was supported by Hu et al.'s and by Renz et al.'s studies which demonstrated significant SI increases only after three contrast enhanced MRIs. (6,15) In contrast to these findings, Roberts et al. reported in a large pediatric cohort of 280 children that for DN hyperintensity at least seven serial injections should be performed. (5) In our study there were some patients with SI increase after three injections, but mostly visible SI increase in the DN was seen after more than 4 repeated injections.

In previous studies, progressive T1-weighted hyperintensities in the DN and GP were associated with the cumulative effect of GBCA. A strong correlation between the number of MRIs performed with gadopentetate dimeglumine and SI ratio changes was reported before. (17,18,19) Kasper et al. reported the number of linear GBCA injections predicted the amount of T1 SI increase for DN in pediatric patients. (20) However, our study did not demonstrate a significant correlation between SI increases in the GP and DN and the number of GBCA enhanced examinations. This may be due to the small number of patients enrolled in the study.

Most studies in the literature are performed with multiple linear contrast agents instead of a specific single

contrast agent. When multiple GBCA is administered, each of their contribution to T1 hyperintensity in the dentate nucleus apartly from others is difficult to determine. The effects of each agent may be different and therefore may not give accurate results. To eliminate this, we focused on one agent exclusively. But this resulted in the decrease of patient population since we had to exclude the patients administered other linear or macrocyclic agents even if only once. Besides, in multiple studies with isolated other linear agents, DN hyperintensity was also shown. In a study held in children with serial administrations of the linear GBCA gadodiamide, there was a significant increase in the mean DN-P SI ratio from the first to the last scan, consistent with gadopentetate dimeglumine (21). Also studies held with both single and mixed linear agents shows gadolinium accumulation in brain.

There are also studies comparing macrocylic agents and linear agents. Renz et al. did not find a T1 SI increase with a macrocyclic agent gadobutrol, whereas they also reported SI increase in the DN with a linear agent, gadopentetate dimeglumine. (15) However, there are controversial results with macrocyclic agents. Few studies have demonstrated SI increases with macrocyclic agents (12)

In some studies SI ratio changes when switching from the gadopentetate dimeglumine to a macrocyclic agent, gadobutrol or gadoterate meglumine were evaluated (22,23). These studies reported a significant decrease in DN:pons (Radbruch et al. 2016; Behzadi et al.2018) and DN:cerebellar peduncle (Behzadi et al. 2018) ratios after the switch to macrocyclic agents. For reproducible results, more studies containing a large group of patients are still needed.

Most previous studies used pons or thalamus as a reference anatomical location for standardization (15,22,24). However, Topcuoglu et al. reported in their study that the T1W SI of both the pons and thalamus were also increased compared with those of the control group and they used CSF as a reference. We also used CSF for reference location and measured GP/CSF an DN/CSF ratios as it might cause more accurate SI measurement.

Advances in surgery, oncology and imaging resulted in increased cure rates in childhood cancers. Gadolinium retention in adult brain was proved histologically and this causes suspicions about the safety especially in this group of pediatric patients who has repeated MRI examinations for intermittent follow-up. Up to date, harmful effects of gadolinium in clinical practice has not been shown and the long term results are unknown. Welk et al. evaluated the association between gadolinium exposure and parkinsonism in the GP. In their study they found no significant difference between patients with Gd-enhanced MRI and non-Gd enhanced MRIs in terms of parkinsonism. Perrotta et al. examined the relation between clinical cerebellar syndrome and gadoterate exposure. They did not detect any finding of cerebellar toxicity. More future studies are needed to investigate the correlation of Gd exposure and clinical outcomes.

There were some limitations of the current study. First, the study group was small and future studies with larger numbers of patients are needed. Second, an age-matched control cohort of patients who did not receive any GBCA was not included and finally, the retrospective design of the study was another limitation.

Conclusion

There was no significant T1 SI increase in the brains of children with at least two gadopentetate dimeglumine administrations but after multiple administrations, significant T1 SI increase was found in this series. While the clinical significance of gadolinium retention in developing pediatric brain is currently unknown, it is important to avoid unnecessary use of linear GBCAs and select the safer agent.

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