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Original Article

Lack of T1 Nuclear Hyperintensity in Pediatric Patients using a Macrocyclic Gadolinium Contrast Agent: Re-visit & Updated Review

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Abstract

Purpose

T1 hyperintense dentate nuclei (HDN) and globus pallidi (HGP) has been recently established as markers of Gadolinium deposition in the brain. This has triggered many studies and a safety alert. We aimed to re-validate the safety of a macrocyclic Gadolinium contrast agent in pediatric patients and present an update in view of current literature.

Material & methods

Retrospective selection of pediatric patients who received at least 3 intravenous injections of Gadoterate Meglumine for MRI studies with at least 12 months of retention time. Age matched controls were used. Contoured region of interest (ROI) signal intensity ratios for dentate to pons (DN/P) and globus pallidi to thalami (GP/T) were measured. The difference of ratios from initial to last MRI examination and between case and controls were tested using paired t-test.

Results

21 out of 49 cases qualified the inclusion & exclusion criteria. The average cumulative contrast injections received by cases was about 6.8. Most of the cases received at least 4 injections and 19 was the greatest number of injections received by one case. The average chronologic age of the cases was about 5 years. No statistical difference of signal intensity ratios from initial to last MRI study (P=0.57 & P=0.40) as well as compared to the controls (P=39 & P=21).

Conclusions

Multiple contrast enhanced MRI studies can be safely administered macrocyclic Gadolinium agents with no risk of Gadolinium deposition in the brain. Currently, the consensus recommendation is of caution and prevention while favoring macrocyclic agents specifically for pediatric patients. No clear evidence for associated clinical sequela related to Gadolinium deposition.

Introduction

Multiple studies have been recently published, which showed neural deposition of gadolinium as manifested by T1 hyper-intense dentate nuclei (HDN) and T1 hyper-intense globus pallidi (HGP) on follow-up non-enhanced MRI examinations [1-5]. Certainly, there is evidence of deposition in other deeper loci of brain, though in much smaller concentrations, as evidenced by MR imaging [6]. The primary evidence is the presence of nuclear T1 hyper-intensity on MR imaging and unequivocally higher risk of neural deposition when linear gadolinium contrast agents are used [3,7-9]. The deposition is related to intravenous gadolinium administration. However, there is no evidence of deposition after intrathecal administration [10].

These observations have been corroborated by autopsy evaluation via electron microscopy and mass spectroscopy [6,11]. In addition, confounding factors that cause nuclear T1 hyperintensities, such as previous radiation and chemotherapy, have been previously addressed [12,13]. Macrocyclic agents have been shown to result in either minimal or no gadolinium deposition [3]. We want to re-validate the absence of HDN and HGP in pediatric patients with multiple previous intravenous injections of gadoterate meglumine (Guerbet, Netherlands), which is an ionic macrocyclic gadolinium contrast agent and the only gadolinium contrast agent used in our institution for the last nine years.

Our study is of significant interest because there are relatively few pediatric studies in the literature related to this issue [14-19]. Our methodology is specifically tailored towards localization and contouring of dentate nuclei and globus pallidi. In addition, the study subjectively excludes any

intrinsic T1 or T2* signal from other causes. Lastly, this is the first study from the Gulf region of the Middle East. Thus, the variables, such as population and environmental factors, need to be considered in scientific enquiries particularly with regard to patient safety.

Materials and Methods

Case and control selection

This study is an IRB approved retrospective study. The study met the patient's consent waiver exemption.

The inclusion criteria were:

a) Pediatric patients < 15 years of chronologic age,

b) At least 3 MRI examinations with intravenous administration of gadoterate meglumine,

c) At least 12 months of interval between the first and last MRI examination with intravenous contrast agents and,

d) Control patients with at least one standard MRI brain examination but no documented history of MRI examination with intravenous injection of gadolinium-based contrast agents (GDCAs).

The exclusion criteria were:

a) Any evidence that a case subject had an MRI examination with contrast agents other than gadoterate meglumine,

b) A lesion in dentate nuclei, globus pallidi, pons or thalamus.

c) Technically sub-optimal examination limiting evaluation of HDN and HGP.

d) Subjectively visible HDN and HGP on the first MRI examination.

e) Susceptibility in the dentate nuclei and globus pallidi (suggesting hemorrhage or calcification).

A data base search was performed using the institutional electronic medical record (EMR) and picture archiving system (PACS). The search criteria were as follows: a) pediatric patients equal to or less than 15 years of age irrespective of gender and ethnicity; b) available MRI examinations on the PACS for review and analysis. The selection criteria strictly followed the abovementioned inclusion and exclusion requirements.

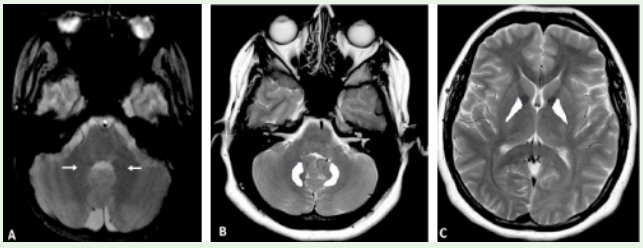

Figure 1: 10 year's old female as a control patient. Axial gradient echo T2 images (A) show lack of susceptibility in dentate nuclei (arrows). Axial FSE T2 images demonstrate demarcated dentate and globus pallidi nuclei (white color coded- B&C).

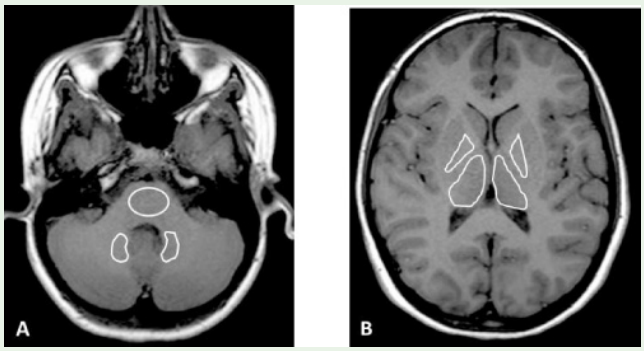

Figure 2: 12 year's old male as a control patient. Axial SE T1 images showing contoured regions of interest (ROI) to determine signal intensity ratios of dentate to pons (DN/P) (A) and globus pallidi to thalami (GP/T) (B).

MRI techniques

All included examinations were performed using 1.5T MRI (Philips, Netherlands), except for 2 cases, the examination of which was performed using 3T MRI (GE, Illinois, USA) in both the subject and the control. The following technique was primarily used for axial T1 SE images using the 1.5T system: (TE-15, TR-500, FA-69, Averages-1, FOV-23 cm, Matrix- 320×288, Display reconstructed slices 4×4.5 mm). The average dose of intravenous gadoterate meglumine received by a subject for individual examination was 0.1 mmol/kg.

MRI Image Review and Analysis

The MRI examinations were reviewed by a board-certified neuro-radiologist. Axial T1 pre-and post-contrast MRI brain images constituted the primary sequence for subjective and objective evaluation of nuclear T1 hyperintensity in the dentate nuclei and globus pallidi.

The reviewer analyzed the non-enhanced axial T1 images from the initial and last examination of the cases and the only included examination of each control subject. Manual ROIs were drawn, centered and contoured to the dentate nuclei (DN), globus pallidi (GP), central pons (P) and thalami (T). These were supplemented by review of axial FSE T2 and GRE T2* or susceptibility-weighted images for the two-fold purpose of identifying the nuclei of interest and ruling out nuclear susceptibility, respectively (Figure 1).

The mean value of signal intensity from each contoured and customized ROI was recorded from each examination followed by calculation of dentate/pons (DN/P) and globus pallidus/thalamus (GP/T) ratios (Fig.2).

Data analysis

Paired t-test was used for statistical data analysis. To compare the T1 signal change, the test required the mean of the difference in ratios (DN/P and GP/T) between the initial and last examinations of the cases.To compare the case and the controls, the test required the mean of the difference of the ratios (DN/P and GP/T) from MRI examinations between the control and case subjects. Standard

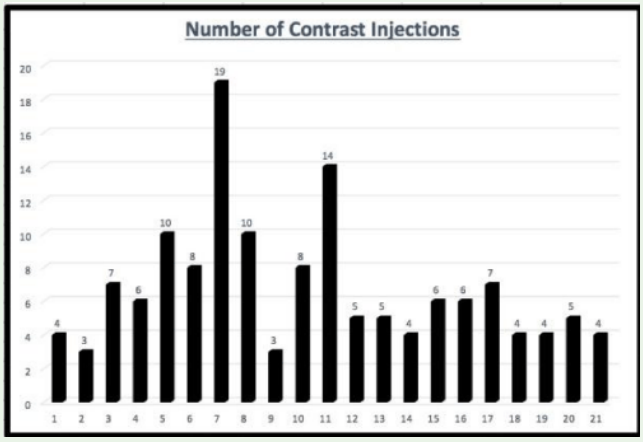

Figure 3: 1Distribution of cumulative contrast injections received by each case.

deviation and standard error of the mean was followed by t-score calculation to test null hypothesis.

Results

Approximately 49 cases were identified in the data bases, which filtered into 21 cases that strictly met the inclusion and exclusion selection criteria. The control consisted of age-matched 21 individuals who underwent at least one non-contrast MRI brain examination.

The mean number of gadolinium injections received by the individuals was 6.8 (Figure 2,3). All of them received at least 4 or more injections over at least one year span except for two cases. The highest number of cumulative contrast injections received by an individual was 19. The average age of the subjects was approximately 64 months (5 years).

There was no statistical difference in the nuclear T1 signal intensity from initial to last MRI examination by comparing T1 signal ratios of dentate to pons (DN/P) (P= 0.57) and globus pallidus to thalamus (GP/T) (P= 0.40). As evident in Figure 4, there is no significant deviation from zero in the ratio difference.

There was no statistical difference in the nuclear T1 signal intensity between the last MRI examination of the cases and single MRI examinations of the control subjects by comparing T1 signal ratios for dentate to pons (DN/P) (P= 0.39) and globus pallidus to thalamus (GP/T) (P= 0.21). As evident in Figure 5, there is no significant deviation from zero in the ratio difference.

Discussion

Gadolinium, as a chelating agent, has been in use as an exclusive MRI contrast agent for more than 3 decades, acclaiming a high safety profile [20]. Gadolinium deposition in animals has been known [21] but did not translate into a significant risk to the human bodies until the discovery and serious alert of Nephrogenic System Fibrosis (NSF) in 2006, due to gadolinium deposition in patients with chronic renal insufficiency [22,23]. Kanda et al. [1,2] followed by many other authors published landmark papers alerting the medical community about deposition of gadolinium contrast agents in the deep nuclei of the brain [1-5]. The surrogate marker of gadolinium deposition in this set of literature has been T1 hyperintense dentate nuclei (HDN) and T1 hyperintense globus pallidi (HGP). The evidence clearly shows a much higher risk of deposition with linear GDCAs while the risk is minimal to none with macrocyclic agents [3,4,24,25]. In addition, this has been confirmed in pediatric population [14-16,26].

Linear gadolinium contrast agents include six of the nine gadolinium agents approved for use to enhance MR Imaging. There is a high correlation of nuclear T1 hyperintensity with cumulative administrations of linear agents [1,4,27,28]. Linear agents are less stable. Therefore, T1 hyperintensity, as a marker of gadolinium, negatively correlates with stability of the contrast agents [3]. However, macrocyclic agents, as more stable compounds, fail to show increased or increasing T1 hyperintensity with multiple injections [14,24,25,28]. Though there are many factors influencing the preference for different MR contrast agents, the two major ones include T1 hyperintensity (means contrast enhancement) and lesseradverse effects. However, the advent of "deposition revelation" has re-invigorated the significance of "in-vivo stability" of the agents and, thus, tilted the balance in favor of macrocyclic agents [3,4,7,29,30]. Our study re-attested the un-equivocal safety of a macrocyclic agent in terms of neural-deposition in the brain. The study clearly revealed that the T1 signal intensity in the deep nuclei (dentate nuclei of cerebellum and globus pallidi of basal ganglia) in the last MRI examination of each case was not statistically or subjectively different than the T1 signal on initial exam or compared to the control subjects. We made sure that the nuclei are well demarcated and distinguished by the lack of intrinsic T1 signal or susceptibility.

The nuclear accumulation of gadolinium correlates with the number of intravenous injections [2,31]. This translates into

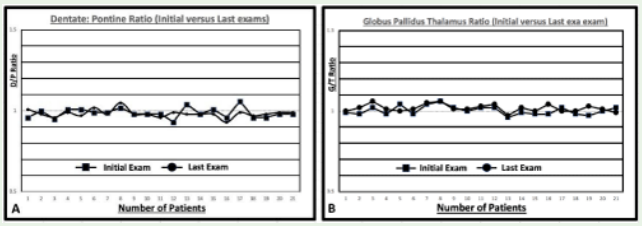

Figure 4: Comparative line graphs of the nuclear T1 signal intensity ratios between initial and last MRI examinations depicting no significant deviation of the difference from zero.

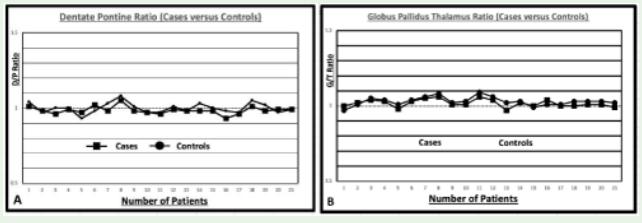

Figure 5: Comparative line graphs of the nuclear T1 signal intensity ratios between cases and controls depicting no significant deviation of the difference from zero.

cumulative dose, traces of which can result in neural deposition. However, the cumulative deposition risk is asymmetric with linear agents [7,31]. Radbruch et al. [28] showed lack of significant nuclear T1 hyperintensity in subjects who underwent an average of approximately 23 macrocyclic agent administrations or even up to 52 individual injections in another study [25]. Similar to our results, gadoterate failed to show T1 nuclear hyperintensity in few other studies [14,15]. The average number of administrations of gadoterate in our study was 6.8. Radbruch et al. [14] showed similar results in pediatric patients with the same agent. However, the average number of administrations was approximately 8.6. The largest number of doses received by one of our pediatric patient was 19.

The cases requiring multiple contrast enhanced MRI exams in our study were mostly pediatric gliomas or neurofibromatosis type 1. These pediatric groups of patients who require long term follow-ups with contrast-enhanced MRI examinations are at high risk for deposition of gadolinium in the brain. Certainly, the potential time span for receiving multiple contrast doses is going to be longer in pediatric population. The preference for macrocyclic agents over linear agents can significantly mitigate or nullify this risk. There is an active trend of switching to macrocyclic agents particularly in pediatric hospitals [32]. It is well established that linear agents cause gadolinium deposition in adults and potentially in the pediatric population, though with limited evidence in the pediatric patients [14,16,26]. Nevertheless, the preferential use of macrocyclic agents in pediatrics is already prevalent.

There has been an increasing awareness about the higher risk of gadolinium deposition in patients with renal insufficiency since the discovery of NSF. Similarly, renal function affects the rate of gadolinium deposition in the brain specifically after administration of linear GBCAs. Patients on hemodialysis showed a significantly higher nuclear T1 signal compared with the patients with normal renal function [33-35]. Fortunately, chronic renal diseases are relatively uncommon in pediatric population. None of our subjects were on dialysis.

The main question is the clinical significance of gadolinium deposition in the brain. The mounting literature is resulting in "gadolinium-phobia". However, to date, there is no solid evidence to argue in favor of clinical toxicity or to directly attribute even minimal clinical stigmata or sequela to gadolinium deposition. Perrotta et al. showed no de novo clinical cerebellar syndrome following repeated administrations of gadoterate (the same contrast agent used in our study) [36] . The clinical significance of the retained gadolinium, if any, remains unknown [37,38]. Furthermore, there is deposition of gadolinium in the vessel walls in autopsy specimens. However, there is no reactive pathologic changes despite high concentrations of gadolinium in dentate nuclei[39].

Certainly, there were few limitations in our study. The first limitation is that our study included a relatively small number of cases. The second limitation is that this was a retrospective study. The third limitation is that the confounding effects of therapy were not factored in because radiation therapy contributes to increased T1 signal in the deep nuclei [12,13]. However, this appears to be irrelevant in our study because there were no subjective or objective increased T1 signal intensities.

It is noteworthy that this is the first study originating from the Middle East and the Gulf region that highlights the safety of a macrocyclic agent in terms of deposition in the brain.

Conclusion

Multiple contrast-enhanced MRI studies can be safely performed with intravenous administration of macrocyclic gadolinium agents with no risk of gadolinium deposition in the brain. Currently, the consensus recommendation is of caution and prevention while favoring macrocyclic agents specifically for pediatric patients. There is no clear evidence for the associated clinical sequela related to gadolinium deposition.

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