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Can unenhanced brain magnetic resonance imaging be used in routine follow up of meningiomas to avoid gadolinium deposition in brain?

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ABSTRACT

Purpose: We hypothesized that unenhanced brain MRI can be used in follow up of patients with intracranial meningioma to avoid gadolinium deposition in the brain and allow measurement of meningioma dimensions from pre-contrast T2-weighted images.

Methods: Dimensions of meningiomas were measured on pre-contrast T2, post-contrast T1 weighted images.

Results: The sizes of meningiomas in post-contrast axial T1-weighted images were similar with that in pre-contrast axial T2-weighted images. Signal intensity increase was detected in dentate nucleus and globus pallidus ($P < 0.05$).

Conclusion: Gadolinium deposition could be avoided in patients with meningioma by using unenhanced brain MRI for follow up scans.

1. Introduction

Meningiomas arise from arachnoid gap cells; they are the most common type (13%–26%) of non-glial primary intracranial tumor [1,2], and mostly occur in the sixth or seventh decades [3,4]. Almost 90% of cases occur in the supratentorial compartment, and the female-to-male ratio is 2:1 [1]. According to the World Health Organization (WHO) histological classification, approximately 90% of meningiomas are benign (WHO grade I), 5%–7% are atypical (WHO grade II), and 1%–3% are malignant (WHO grade III) [5]. They are usually found incidentally by brain magnetic resonance imaging (MRI) or computed tomography performed for other reasons [5]. Symptomatic cases present clinically with headache, personality changes, paresis, and seizures [1]. On brain MRI scans, meningiomas are extra-axial, dural-based, well-defined tumors that are mostly isointense with gray matter on T1- and T2-weighted images and show homogenous and prominent (> 95%) enhancement after intravenous contrast media injection. Post contrast images increase diagnostic reliability of meningiomas by showing homogenous and prominent enhancement, dural tail, vascular clefts [6,7]. It has been reported that 60% of asymptomatic meningiomas [6,8] and calcified meningiomas [5,9] show no tumor growth. In practice most clinicians administer a conservative treatment for asymptomatic meningiomas, with contrast-enhanced brain MRI every 6 months to a year in routine follow ups [1,2,5] to evaluate the lesion growth; the dimensions of the lesion are usually measured on post-contrast T1-weighted images and compared with previous scans.

Gadolinium-based contrast agents (GBCA) are used for enhanced brain MRI owing to the paramagnetic effect of gadolinium ion. Free gadolinium is toxic in biological systems; chelated forms must therefore be used to avoid toxicity. GBCAs are classified as linear non-ionic, linear ionic, macro cyclic non-ionic, and macro cyclic ionic. Linear forms are the most frequently used; an increased signal intensity in the dentate nucleus (DN) and globus pallidus (GP) was observed in pre-contrast axial T1-weighted images in consecutive MRI scans using linear GBCAs in patients without renal dysfunction [10–12]. Others have reported gadolinium deposition in postmortem brain tissue following repeated use of linear GBCA independent of renal function [13,14]. T1 hyper intensity in the DN and GP has been linked to gadolinium deposition [13]. McDonald et al. injected multiple doses of linear and macro cyclic gadolinium based contrast agents to rats and found out those macro cyclic agents also deposits in brain which was two to four times lesser than linear agents [15].

The clinical effect of the gadolinium deposition in the brain is unknown. To the best of our knowledge in none of the previous studies gadolinium deposition in the brain was found to be associated with any clinical symptom [10,12,14].

We hypothesized that unenhanced brain MRI can be used in routine follow up of patients with intracranial meningioma in order to avoid

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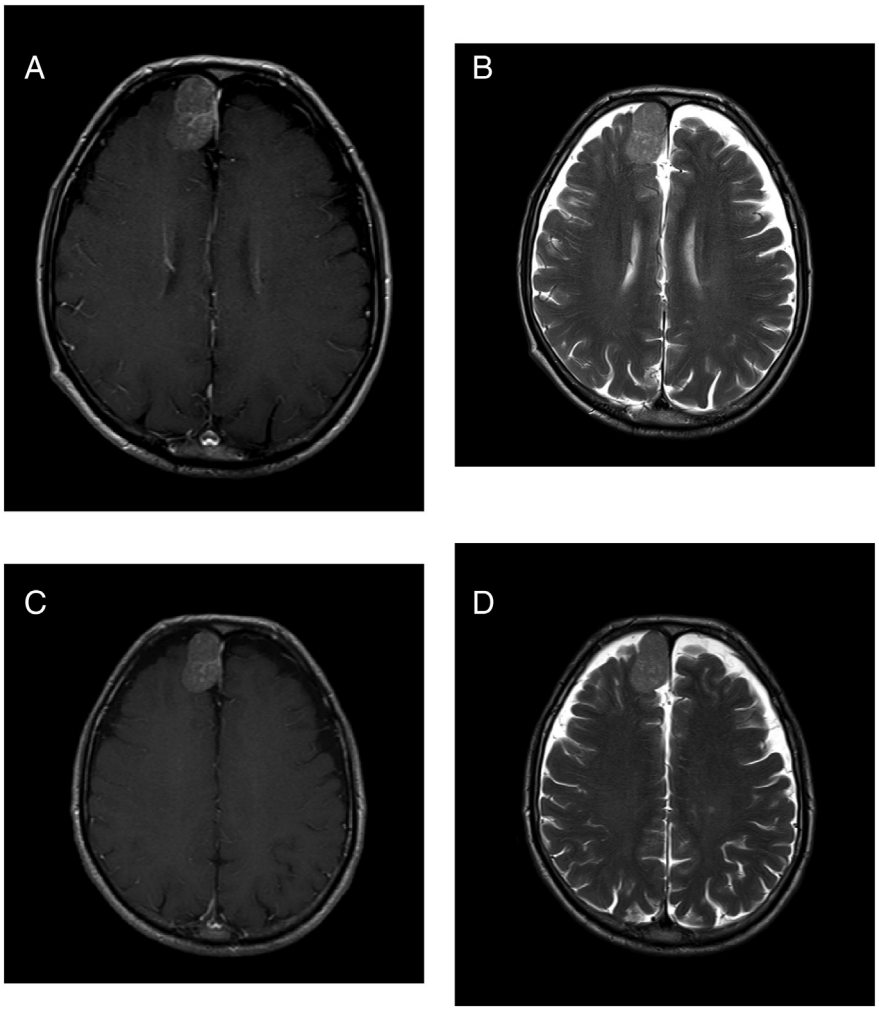

Fig. 1. 69 year old male patient with frontal meningioma who underwent 6 enhanced brain MRIs with linear GBCA. Axial post-contrast T1 weighted (A), axial pre-contrast T2 weighted images (B) from the first brain MRI and axial post-contrast T1 weighted (C) and axial pre-contrast T2 weighted (D) images from the last brain MRI. The lesion size was measured as 32 × 21 mm (apxml) on axial T1-weighted image (A) and 32 × 20 mm on axial T2-weighted image (B) at the initial brain MR imaging. The lesion size was measured as 32 × 20 mm (apxml) on axial T1-weighted image (C) and 32 × 20 mm on axial T2-weighted image (D) at the sixth brain MR imaging. The measurements are congruent and there is no progression in the meningioma.

gadolinium deposition in the brain and allow measurement of meningioma dimensions from pre-contrast T2-weighted images. We investigated whether measurements on pre-contrast T2-weighted images and post-contrast T1-weighted images are congruent. We calculated the signal intensity ratios for DN/pons, DN/cerebellum and GP/thalamus from the precontrast T1 weighted images if the signal intensity of globus pallidus and dentate nucleus increases with the usage of linear gadolinium based contrast agents which is linked to gadolinium deposition.

2. Materials and methods

2.1. Patient population

From November 2010 to October 2016, we retrospectively evaluated 29 patients (age range: 26–86 years; median age: 61 years; 21 women, 8 men) in a routine follow up for intracranial meningioma who underwent consecutive brain MRI with linear non-ionic GBCA (gadoversetamide) at our institution. The study was approved by the local ethics committee. Of the 29 patients, 26 had five and three had six enhanced brain MRIs. A standard dose of 0.1 mmol/kg or 0.2 ml/kg of non-ionic contrast material was administered intravenously. The mean time interval between brain MRIs was 10 months (range: 1.66–21.3 months).

A total of 28 patients had one meningioma and one patient had two meningiomas. Exclusion criteria were: (1) an estimated glomerular filtration rate lower than 60 ml/min; (2) a history of brain hemorrhage, brain irradiation, brain surgery, intracranial infection such as meningitis or encephalitis, demyelinating diseases, or metabolic diseases; (3) a history of malignancy or chemotherapy; and (4) the existence of hepatic dysfunction.

2.2. MR imaging parameters and data analysis

MRI was performed on a 1.5 T MRI scanner (Avanto; Siemens, Erlangen, Germany) with a 16-channel phased array head coil. The standard MR imaging protocol included axial FLAIR (repetition time/echo time [TR/TE]: 8000/84 ms, slice thickness: 5.5 mm, field of view [FOV]: 22 cm); axial T1-weighted images (TR/TE: 410/9.2 ms, slice thickness: 5.5 mm, FOV: 22 cm); axial T2-weighted images (TR/TE: 3630/103 ms, slice thickness: 5.5 mm, FOV: 22 cm); post-gadolinium-enhanced axial T1-weighted images; (TR/TE: 552/17 ms, slice thickness: 5.5 mm, FOV: 22 cm). A standard dose of gadoversetamide (0.1 mmol/kg or 0.2 ml/kg) was intravenously administered as a bolus. Scans were visually evaluated by a neuroradiologist with 6 years of experience.

Meningioma dimensions were measured on axial pre-contrast T2-weighted images and axial post-contrast T1-weighted images based on anterior-posterior (AP) and medial-lateral (ML) lengths on the first and last scans. The measurements were made by two neuroradiologists 10 years and 6 years experienced in neuroradiology. The measurements were made independently the neuroradiologists were blinded to the names of the patients and the dates of the brain MRIs. The first and last measurements were compared to determine lesion growth. Measurements on post-contrast T1- and pre-contrast T2-weighted images were evaluated for correlations.

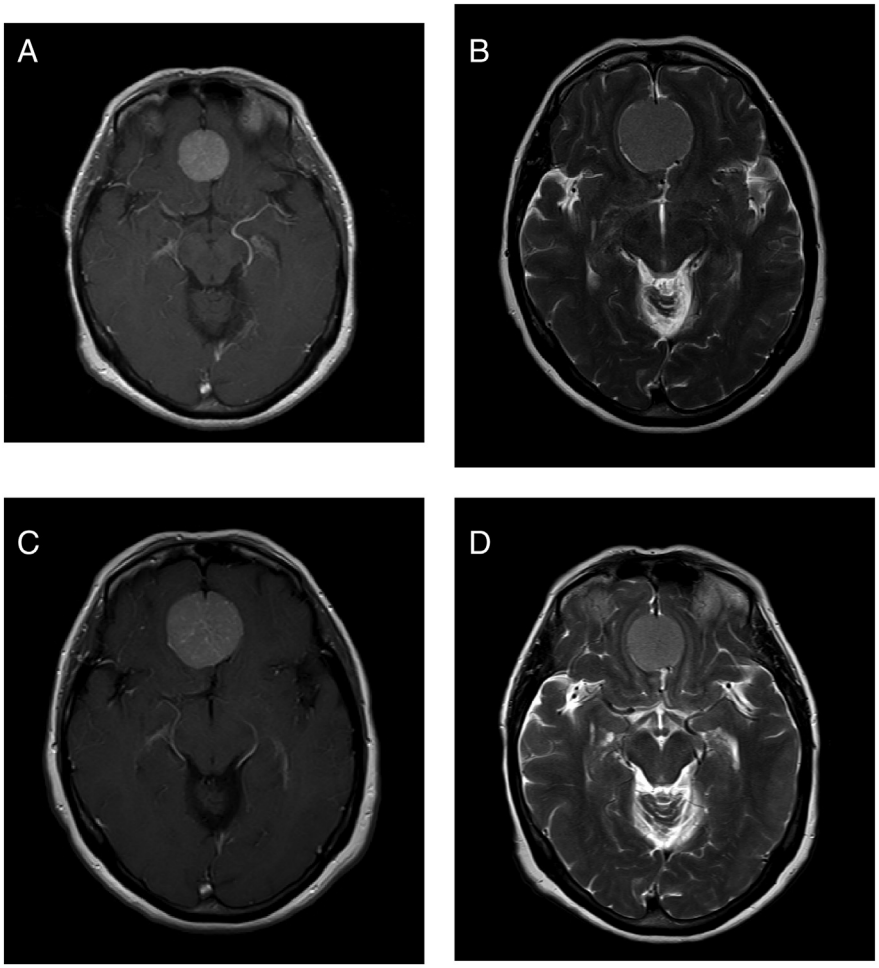

Fig. 2. 76 year old female patient with frontal meningioma who underwent 6 enhanced brain MRIs with linear GBCA. Axial post-contrast T1 weighted (A), axial pre-contrast T2 weighted images (B) from the first brain MRI and axial post-contrast T1 weighted (C) and axial pre-contrast T2 weighted (D) images from the last brain MRI. The lesion size was measured as 28 × 26 mm (apxml) on axial T1-weighted image (A) and 26 × 28 mm on axial T2-weighted image (B) at the initial brain MR imaging. The lesion size was measured as 35 × 36 mm (apxml) on axial T1-weighted image (C) and 35 × 37 mm on axial T2-weighted image (D) at the sixth brain MR imaging. The measurements show correlation. There is progression in the meningioma which can be both shown by axial post-contrast T1 weighted images and axial pre-contrast T2 weighted images.

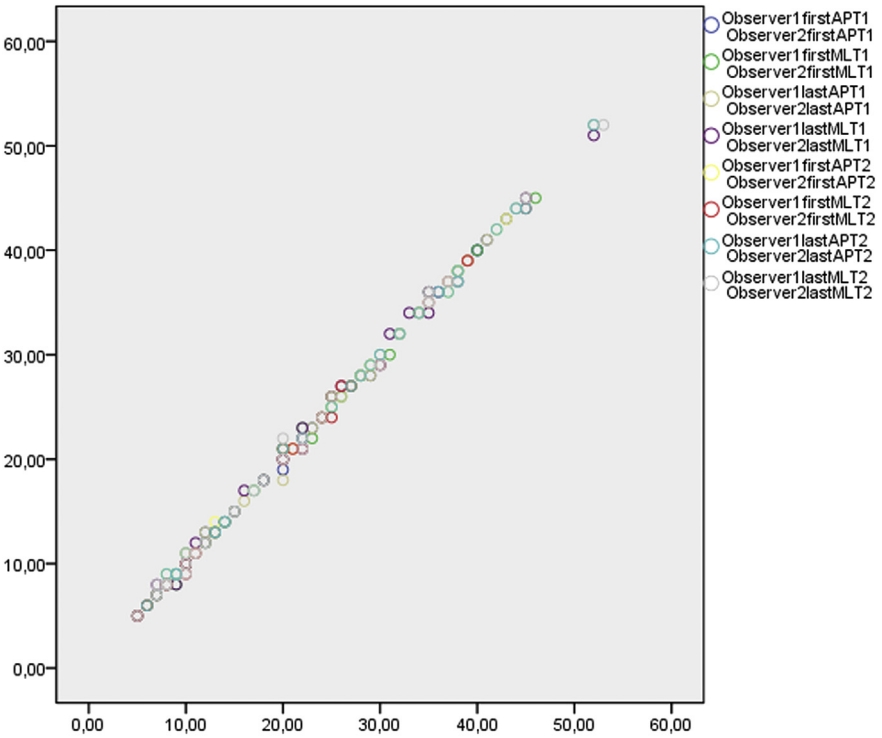

Fig. 3. Scatter plot diagram shows the dimensions of meningiomas measured by observer 1 versus observer 2 from the first and last brain MRIs on axial postcontrast T1 weighted images and axial precontrast T2 weighted images. $R^2 = 0.99$.

Table 1
Age, gender, lesion localization, follow up time for each lesion and the dimensions of meningiomas measured from the first and last MRIs on both pre-contrast axial T2 weighted images and post-contrast axial T1 weighted images. The dimensions are consensus of the two readers.

Age	Gender	Lesion localization	Mean follow up time (month)	Dimensions on first MRI postcontrast T1W I (mm × mm)	Dimensions on first MRI precontrast T2W I (mm × mm)	Dimensions on last MRI postcontrast T1W I (mm × mm)	Dimensions on last MRI precontrast T2W I (mm × mm)
70	F	Infratentorial	5	38 × 23	36 × 18	38 × 23	36 × 17
80	F	Infratentorial	10	14 × 7	14 × 6	14 × 8	14 × 7
68	F	Supratentorial	14	40 × 45	39 × 44	45 × 51	44 × 52
61	M	Supratentorial	22	10 × 8	9 × 8	11 × 7	9 × 8
49	F	Supratentorial	17	29 × 24	26 × 24	27 × 24	26 × 24
64	M	Infratentorial	19	38 × 12	37 × 12	38 × 13	38 × 12
72	F	Supratentorial	38	41 × 30	42 × 29	41 × 32	42 × 29
42	F	Supratentorial	23	10 × 8	9 × 8	10 × 9	9 × 8
57	F	Supratentorial	32	12 × 10	12 × 10	12 × 10	12 × 10
58	M	Supratentorial	32	28 × 22	29 × 21	28 × 21	29 × 21
86	F	Supratentorial	24	23 × 26	21 × 24	30 × 34	28 × 31
86	F	Supratentorial	24	40 × 40	38 × 39	52 × 45	52 × 45
71	M	Supratentorial	27	43 × 38	43 × 37	44 × 39	44 × 37
26	F	Infratentorial	47	21 × 22	21 × 21	21 × 22	21 × 21
57	F	Supratentorial	30	22 × 20	21 × 20	23 × 20	22 × 20
32	F	Infratentorial	44	19 × 18	17 × 18	18 × 18	17 × 17
64	F	Supratentorial	34	7 × 8	7 × 8	7 × 8	7 × 8
55	F	Supratentorial	36	6 × 5	6 × 5	6 × 5	6 × 5
81	F	Infratentorial	60	28 × 26	28 × 26	28 × 27	28 × 26
50	F	Supratentorial	36	14 × 14	13 × 13	20 × 20	18 × 18
65	F	Supratentorial	50	28 × 26	26 × 28	35 × 36	35 × 37
60	F	Supratentorial	42	10 × 10	8 × 11	10 × 10	8 × 11
76	F	Supratentorial	44	29 × 25	29 × 24	38 × 34	37 × 32
36	F	Supratentorial	46	13 × 10	13 × 9	13 × 10	13 × 9
62	F	Infratentorial	47	34 × 36	34 × 35	34 × 36	34 × 36
48	F	Supratentorial	66	15 × 11	15 × 10	16 × 12	15 × 11
55	F	Supratentorial	60	27 × 17	25 × 15	26 × 17	25 × 15
84	F	Infratentorial	60	12 × 8	13 × 7	12 × 8	13 × 8
69	M	Supratentorial	61	32 × 21	32 × 20	32 × 20	32 × 20
72	F	Supratentorial	64	8 × 10	9 × 10	8 × 10	9 × 10

Quantitative analysis of images to assess hyper intensity in the DN and GP was carried out as previously described [10,11]. An operator-defined oval region of interest (ROI) was drawn on axial pre-contrast T1 weighted images around the right DN, central pons, right cerebellar white matter, right GP, and right thalamus for each brain MRI. The ROI was first drawn as large as possible on the DN and GP, and the same size was used for the pons, cerebellar white matter, and thalamus. If the right side could not be examined due to artifacts or gliosis, the left side was used. The DN-to-pons signal intensity ratio (DN/pons) was calculated by dividing the mean signal intensity of the DN by that of the pons. The DN-to-cerebellum and GP-to-thalamus signal intensity ratios (DN/cerebellum and GP/thalamus, respectively) were calculated in a similar manner for the respective brain regions.

In total, 148 brain MRI scans were examined for differences in DN/pons, DN/cerebellum, and GP/thalamus signal intensity ratios. In 27 patients, GP/thalamus signal intensity ratios were measured from the right side. In two patients, GP/thalamus signal intensity ratios were measured from the left side due to chronic encephalomalacia in the right basal ganglia. DN/pons and DN/cerebellum signal intensity ratios were measured from the right side.

2.3. Statistical analysis

Data were analyzed using R v.3.2.1 software (R Foundation for Statistical Computing, Vienna, Austria), and the a priori significance level was set to $P < 0.005$. A one-sample *t*-test was used to determine assess differences in mean signal intensity ratios of the first and last examinations. Analyses were carried out for DN/pons, DN/cerebellum, and GP/thalamus ratios. Inter observer correlation agreement between the two readers' tumor measurements from the first and last brain MRIs from axial T1 post contrast and axial T2 pre contrast images was tested using interclass correlation coefficient test.

3. Results

A total of 22 of 30 meningiomas were in the supratentorial region and eight were in the infratentorial region. Meningioma size (AP × ML) varied from 6 × 5 mm^2 to 45 × 40 mm^2. The size of six meningiomas in five patients increased, as determined from measurements on both axial pre-contrast T2-weighted images and axial post-contrast T1-weighted images (Figs. 1 and 2). The mean increase in AP length was 8 mm (minimum 5 mm–maximum 14 mm) and the mean increase in ML length was 7 mm (minimum 5 mm–maximum 10 mm). Measurements on axial post-contrast T1-weighted and axial pre-contrast T2-weighted images were congruent. Inter observer agreement was very high for all measurements (R = 0.99). (Fig. 3) Meningioma dimensions measured on the first and last MRI scans on pre-contrast axial T2-weighted images and post-contrast axial T1-weighted images as well as the follow-up time for each lesion, lesion localization, and demographic findings are shown in Table 1.

A total of 20 meningiomas were isointense on both T1- and T2-weighted images and showed diffuse homogenous contrast enhancement on post-contrast T1-weighted images; 26 had a dural tail and cerebrospinal fluid cleft. In 10 of the meningiomas, calcification was detected as hypo intense areas on T2-weighted images and SWI sequences. There were peritumoral hyper intensities in adjacent brain parenchyma consistent with edema on T2-weighted images in brain MRI scans of two meningiomas. Both lesions showed progression during the follow up but the peritumoral edema did not change. For the remaining 29 lesions, there was no change in intensity in the adjacent brain parenchyma.

Median (IQR) DN/pons ratios for the first and last brain MRI scans were 1048 (0,0475) and 1126 (0,1035) respectively; median (IQR) DN/cerebellum ratios for the first and last brain MRI scans were 1063 (0,05) and 1140 (0,111) respectively; and median (IQR) GP/thalamus ratios for the first and last brain MRI scans were 1073 (0,035) and 1123

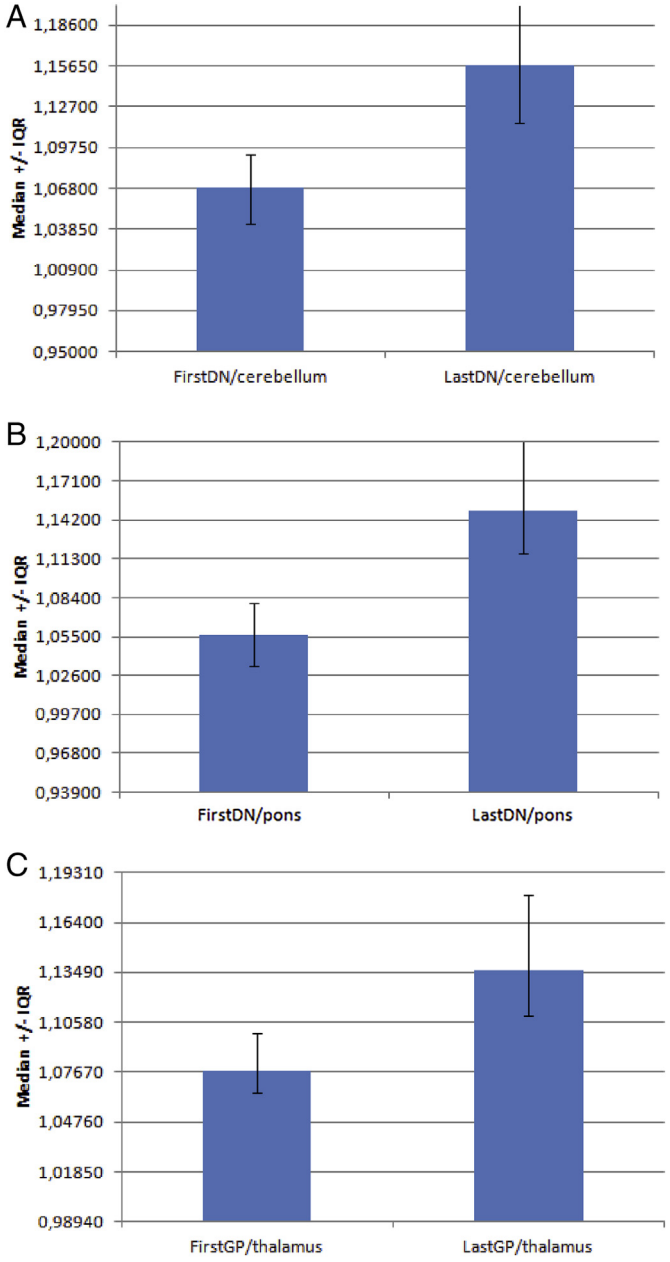

Fig. 4. a. Box plot diagram showing median (IQR) DN/cerebellum signal intensity ratios from the first and last brain MRIs.
b. Box plot diagram showing median (IQR) DN/pons signal intensity ratios from the first and last brain MRIs.
c. Box plot diagram showing median (IQR) GP/thalamus signal intensity ratios from the first and last brain MRIs.

(0,07), respectively. The difference in DN/pons ratio between the first and last scan was significantly > 0 ($P < 0.05$), with a mean value of 0.0931. Similar trends were observed for DN/cerebellum ratio (mean value = 0.0883) and GP/thalamus ratio (mean value = 0.058). The distribution of differences in DN/cerebellum, DN/pons, and GP/thalamus signal intensity ratios between the first and last MRI scan are shown in Fig. 4. High signal intensities were observed in the DN and GP on axial pre-contrast T1-weighted images from a patient who received linear GBCA six times (Fig. 5).

4. Discussion

The major finding of this study is that the size of meningiomas in post-contrast axial T1-weighted images was similar with that in pre-contrast axial T2-weighted images that is, both showed tumor growth. Our results also demonstrate that of DN/pons, DN/cerebellum, and GP/thalamus signal intensity ratios increased with multiple administrations of linear non-ionic GBCAs in patients with normal renal function.

Meningiomas are easily diagnosed by enhanced brain MRI and show typical imaging findings. Since brain MRI is widely used for diverse indications, most meningiomas are diagnosed incidentally. Those that are asymptomatic are routinely followed up with enhanced brain MRI [2], especially in elderly patients with co morbidities [2]. In general the size of the tumor is measured on post-contrast T1-weighted images and compared to that in the previous scan. In most cases untreated meningiomas followed up with brain MRI showed no progression of the lesion, and only a few cases with a tumor size smaller than 2 cm developed symptoms during a median follow up period of 4.6 years, whereas 17% of patients with lesions > 3 cm developed symptoms during the follow up [16]. A study of 60 patients with asymptomatic meningiomas who were followed for 32 months revealed that none of the patients became symptomatic, 35 showed no progression, and 10 showed tumor growth at 2.4 mm/year [17]. In another report, four of 121 meningioma cases showed progression by serial brain MRI; 24 lesions were calcified and none progressed or became symptomatic [18]. In the present study, the median follow up time was 36 months; six meningiomas in five patients showed progression but none of them became symptomatic, and calcified meningiomas did not show progression, which is consistent with previous reports.

Increased signal intensity in the DN and GP on pre-contrast T1-weighted images was previously reported in patients with multiple sclerosis and brain irradiation history [19,20]. It's first reported by Kanda et al. that signal intensity of dentate nucleus on pre contrast T1 weighted images increases with six contrast enhanced brain MRIs with linear GBCAs [10]. Errante et al. found that dentate nucleus to pons signal intensity ratio increases with serial contrast enhanced brain MRI using linear GBCA in patients with multiple sclerosis and brain metastasis [21]. Ramalho et al. found increase in the signal intensity of dentate nucleus after four contrast enhanced brain MRIs with linear GBCA [22]. In the current study we also found increased signal intensity in the DN and GP on pre contrast T1 weighted images after minimum five contrast enhanced brain MRIs with linear GBCA. In the current study the signal intensity increase in dentate nucleus and globus pallidus are similar with the previous studies. Our patients did not have a history of malignancy, head irradiation, or multiple sclerosis, unlike the patients in previous studies.

Gadolinium was found to be stored in the brain tissue of patients who received a minimum of four administrations of non-ionic linear GBCA [14], in the skin of a patient without renal dysfunction who had undergone 61 enhanced MRI scans with GBCAs [23], as well as in the bones [24]. McDonald et al. showed deposition of gadolinium in rats after both multiple and linear macro cyclic GBCA administration and they concluded that tissue deposition of gadolinium after usage of macro cyclic GBCA was lesser than linear GBCAs [24]. Kanda et al. and Radbruch et al. compared linear and macro cyclic GBCAs in different studies. They both found signal intensity increase in the dentate nucleus and globus pallidus on T1 weighted pre contrast images after serial linear GBCA usage but not by the macro cyclic GBCAs [11,12]. In our institution, a non-ionic linear GBCA (gadoversetamide) is routinely used unless the patient has renal dysfunction so we did not compare linear GBCA with macro cyclic GBCA.

The clinical effect of the gadolinium deposition in the brain is unknown. According to our knowledge in none of the previous studies gadolinium deposition in the brain was found to be associated with any clinical symptom. In the current study we did not find any neurological symptom from the medical data of patients. There is e few studies about the value of Positron Emission Tomography (PET) as an alternative imaging technique in the diagnosis, treatment planning and diagnosis of meningioma recurrence [25].

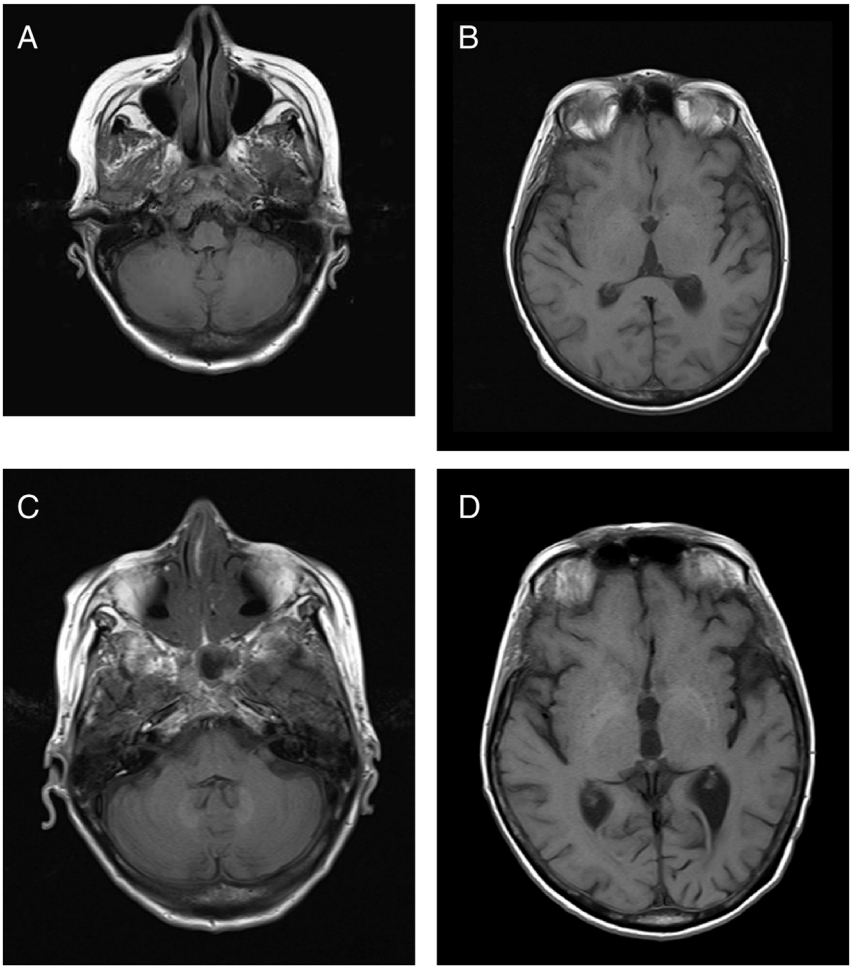

Fig. 5. Axial pre-contrast T1 weighted images showing the typical finding of hyperintensities in DN and GP. Images were acquired from the first MRI (A,B) and sixth MRI (C,D) with linear GBCA.

There are some limitations of the current study firstly our sample size was small, secondly we did not compare the linear gadolinium based contrast agents with macro cyclic gadolinium based contrast agents for deposition.

5. Conclusion

In the current study the size of meningiomas in post-contrast axial T1-weighted images was compatible with that in pre-contrast axial T2-weighted images that is, both showed tumor growth. We also observed gadolinium accumulation in the brain corresponding to the increase in signal intensity in the DN and GP with multiple administrations of linear GBCA. Although the clinical consequences are unknown gadolinium deposition could be avoided in patients with meningioma by using unenhanced brain MRI for follow up scans.

Conflicts of interest and source of funding

There is no conflict of interest.

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