Original Article

Assessment of Age-Related Changes in Normal Clivus Bone Marrow Using Clivus-to-Corpus Callosum Signal Intensity Ratio on Magnetic Resonance Imaging

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Objective: To assess whether the signal intensity ratio of the clivus to corpus callosum (clivus/CC) depends on age.

Materials and Methods: A retrospective study of 244 subjects investigated the magnetic resonance imaging (MRI) appearance of the clivus on T1-weighted sagittal images. Both qualitative and quantitative assessments of MRIs were evaluated. In qualitative assessment, signal intensity patterns of clivus were graded from I to III, according to the proportion of low and high signal intensity areas occupying the clival marrow region. In quantitative assessment, the authors performed multivariable Gaussian regression analysis to assess the association of age categorized by decades and the signal intensity ratio of clivus/CC and clivus to cerebrospinal fluid (clivus/CSF).

Results: Grade I clivus was found in about 40% of the age 1 to 9, whereas Grade III clivus was more frequent at more than 15% in the age over 50. There were statistically different in the mean values of clivus/CSF and clivus/CC signal intensity ratios by grades. The mean values of clivus/CSF and clivus/CC signal intensity ratios were increased by ages in both genders, but slightly higher in males. In unadjusted analyses, the differences in mean values of clivus/CC signal intensity ratio were larger by increasing age. After adjustment for gender, the difference in mean values remained the same.

Conclusion: There was an age-related pattern of clivus bone marrow intensity. Since the use of CC as a new landmark showed a similar pattern as of pons, the ratio of clivus/CC signal intensity may be used as an alternative measurement in brain MRI.

Keywords: Clivus; Bone marrow; Magnetic resonance imaging (MRI); Corpus callosum (CC)

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The clivus is a bony part of the cranium at the skull base and best seen on the midsagittal magnetic resonance (MR) imaging. It resembles a triangle that has its apex located at the anterior margin of the foramen magnum. The central portion of the clivus is composed of the cancellous bone that makes different MR signal characteristics depending on the amount and nature of the marrow elements that change with ages[1,2]. The knowledge on detecting the changes could indicate normal physiology of clivus and may raise concerns on abnormalities on MR imaging.

MR is a highly sensitive procedure and is alternative to plain films, computer tomography (CT), and radionuclide studies for imaging of normal and abnormal marrow. This procedure can differentiate marrow with various conditions such as fatty, fibrotic, cellular, hypercellular, and hemosiderotic marrow[3]. Existing studies reported the proportioning intensity values such as signal intensity ratios of clivus/pons and clivus/CSF, measured at T1-weighted midsagittal cranial image[4,5]. Their report showed that the averages of clivus intensity values corresponded to age groups and gender. Thus, these values can be used to assess abnormalities presented on MR images of the brain, and pons is a good reference structure to compare to MR signal intensity of clivus marrow. Although pons is commonly used, some pathologies may be detected especially in elderly patients. In practice of radiology, corpus callosum (CC) is an interesting structure because it has a homogeneous signal intensity and could be well-visualized on T1-weighted midsagittal

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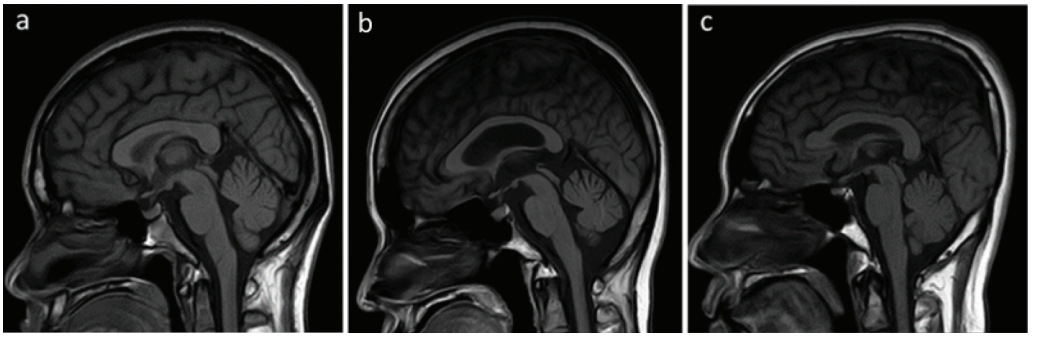

Figure 1. Qualitative assessment (visual grading) of clivus bone marrow on the midsagittal T1-weighted MR image. (a) Grade I normal clivus in a 24-year-old male, (b) Grade II normal clivus in a 46-year-old female, (c) Grade III normal clivus in a 60-year-old male.

cranial images as well. Assessing the proportioning intensity values on this structure may gain insights in using CC as an alternative landmark to pons to evaluate MR imaging of the brain.

Therefore, the purpose of the present study was to evaluate the signal intensity of clivus bone marrow from MR imaging using CC as a landmark and to assess whether the signal intensity ratio of clivus to CC depends on age.

Material and Methods

The present study was approved by the Naresuan University Institutional Review Boards (IRB No.1008/62). Informed consent was waived based on retrospective study and minimal patient risk. The medical records of 1,717 subjects between January 2015 and October 2019 were reviewed. Patients who had undergone brain MR imaging at Radiology Department were included in the present study. The authors excluded the patients who were 1) younger than one year old because of having immature myelination process of CC, 2) older than 79 years old because of having aging brain or abnormal brain imaging, and 3) diagnosed with known diseases involving the skull base or bone, as well as those who had systemic diseases or had previous radiation therapy, chemotherapy, or intracranial surgery. The authors performed stratified random sampling with respect to the age categories divided by decades as 1 to 9, 10 to 19, 20 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, and 70 to 79 years. The sample size of patients in each age category was about 30% of the original number of patients in each age category. Two hundred forty-four subjects were eligible for the MR appearance of the clivus on T1-weighted sagittal image study.

Imaging procedures

All MR examinations were performed with a 1.5-T MR scanner (Philips Ingenia, Philips Medical Systems, Best, the Netherlands) by using a head coil. The imaging protocol included standard spin-echo T1-weighted midsagittal image (TR 500 to 600 msec, TE 11 to 17 msec, 5 mm section thickness, 21 cm field-of-view, number of signal acquisitions 1 to 2, and a 192×192 matrix size). T1-weighted midsagittal cranial image was chosen for examination. In this view, midline structures such as the clivus, the CC (genu), and the fourth ventricle were observed on the same plane. The CC and the cerebrospinal fluid (CSF) were chosen as reference landmarks with stable MR signal intensity values in subjects without disease involving them. Both qualitative and quantitative assessments of MR images were reviewed by three radiologists (WG, NO, ST) blinded to the information related to the images such as subject's name, age, and gender.

Assessment of clivus signal intensities

For the qualitative assessment, the signal intensity of clival bone marrow was visually graded from Grade I to III according to the proportion of low and high signal intensity areas occupying the clival marrow region. This grading system was previously used by Kimura et al[6]. Grade I referred to predominantly low signal intensity, occupying more than 50% of the clivus, Grade II referred to low signal intensity portion occupying less than 50% but greater than 20% of clivus, and Grade III referred to predominantly high signal intensity, with some low signal intensities, occupying less than 20% of the clivus (Figure 1). The authors made the consensus grading given by the three radiologists. In case of disagreement of readings among radiologists, the majority of voting and consensus-based discussion were made.

For the quantitative assessment, the authors used

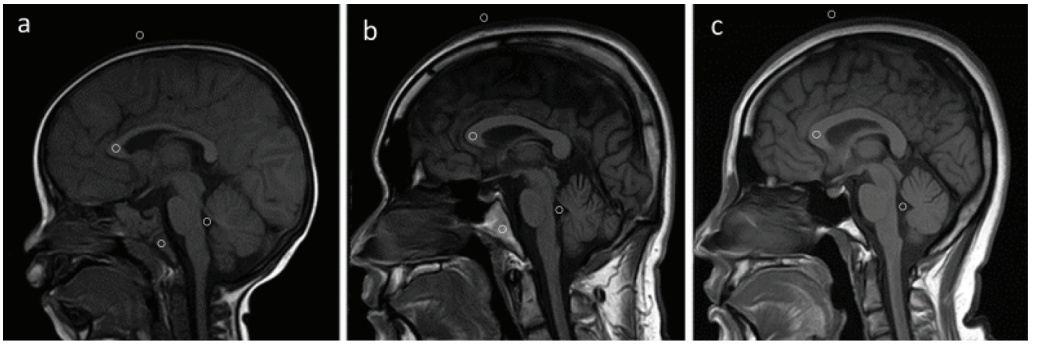

Figure 2. Quantitative assessment of clivus bone marrow by drawing the white circle at the region of interest (clivus, CC, CSF, and the background noise) on the midsagittal T1-weighted MR image. (a) In a 1-year-old girl, (b) In a 30-year-old male, (c) In a 32-year-old female.

the signal intensity values for the region of interest (ROI) in the clivus, CC, CSF, and the background noise. The background noise represented by air adjacent to the vertex at a level corresponding to the clivus, was subtracted from the signal intensity values measured from the clivus, CC, and CSF. One of the present study radiologists (NO) placed and checked the circular ROI. The center of clivus, CC, and the fourth ventricle were used as the three main locations of ROI in the present study. The circular ROI was standardized by the size of the area to be measured as 0.10 cm^2 as to avoid the area of the cortical bone within the ROI (Figure 2). These data were then used to calculate the signal intensity ratios of 1) clivus to CC (clivus/CC) and 2) clivus to CSF (clivus/CSF).

Statistical analysis

Descriptive statistic for categorical variables was presented as frequencies and proportions. Mean and standard deviation (SD) were used to summarize continuous variables. The authors compared the mean values of clivus/CSF and clivus/CC signal intensity ratio by the grading intensity using one-way ANOVA with equal variances. Barrett's test was used to assess the equality of the variances. Multivariable Gaussian regression analysis was performed to examine the relationship of the mean values of clivus/CC signal intensity ratio and age categories. The category of 1 to 9 years was used as a reference category in the regression analyses. The beta-coefficients (β) from the regression model represented the difference in the mean values of signal intensity ratio. All statistical analyses were performed using Stata version 12.1 and R Studio version 4.0.2. The significance level (α) was set at less than 0.05.

The three radiologists reviewed all brain imaging. The authors reported a good interrater agreement on MR imaging reading of normal clivus in the authors' previous research[7].

Table 1. Graded MR signal intensity of normal clivus bone marrow related to age

	Total (n=244)	Grade I (n=43); n (%)	Grade II (n=148); n (%)	Grade III (n=53); n (%)
Sex				
Female	121	23 (53.5)	74 (50.0)	24 (45.3)
Male	123	20 (46.5)	74 (50.0)	29 (54.7)
Age (years)				
1 to 9	33	16 (37.2)	17 (11.5)	0 (0.0)
10 to 19	31	8 (18.7)	19 (12.8)	4 (7.6)
20 to 29	30	5 (11.6)	22 (14.9)	3 (5.7)
30 to 39	30	5 (11.6)	15 (10.1)	10 (18.9)
40 to 49	30	3 (7.0)	20 (13.5)	7 (13.2)
50 to 59	30	4 (9.3)	17 (11.5)	9 (17.0)
60 to 69	30	2 (4.6)	16 (10.8)	12 (22.6)
70 to 79	30	0 (0.0)	22 (14.9)	8 (15.0)

Results

Qualitative assessment

The distributions of gender and age of the study subjects by the MR signal intensity grading of normal clivus bone marrow are shown in Table 1. Grade I was more reported in 53.5% (n=23) of females, whereas Grade III was more in 54.7% (n=29) of males. Grade I was found more frequently in the younger ages, while Grade III clivus was more frequent in the older ages. Grade I clivus was found 37.2% (n=16) of the subjects aged 1 to 9 years, and less than 10% of the age over 40 years. Grade III was found more than 10% in each age group over the age of 30 years, with the highest proportion of 22.6% (n=12) at the age of 60 to 69 years. Grade II was equally distributed across all age groups, at 10% to 15%.

Table 2. Descriptive values of clivus/CSF and clivus/CC intensity ratios in all individuals according to the grades

	Grade I (n=43); mean±SD	Grade II (n=148); mean±SD	Grade III (n=53); mean±SD	p-value
Clivus/CSF	2.95±0.82	4.59±1.07	5.88±1.15	<0.001*
Clivus/CC	1.15±0.33	1.86±0.44	2.39±0.46	<0.001*

CSF=cerebrospinal fluid; CC=corpus callosum; SD=standard deviation

* One-way ANOVA with equal variances

Table 3. Descriptive values of clivus/CSF and clivus/CC intensity ratios comparatively for each age group in males and females

Age (years)	Clivus/CSF; mean±SD		Clivus/CC; mean±SD	
	Female (n=121)	Male (n=123)	Female (n=121)	Male (n=123)
1 to 9	2.65±0.58	3.13±0.72	0.99±0.25	1.22±0.29
10 to 19	3.89±1.10	4.03±1.13	1.52±0.42	1.57±0.48
20 to 29	4.14±0.89	4.24±1.08	1.58±0.34	1.66±0.38
30 to 39	4.52±1.03	5.13±1.04	1.75±0.39	2.08±0.34
40 to 49	4.48±1.53	4.73±1.02	1.83±0.48	2.01±0.47
50 to 59	5.19±1.11	4.88±1.20	2.03±0.40	2.04±0.45
60 to 69	5.67±1.12	5.77±1.61	2.28±0.41	2.38±0.64
70 to 79	5.72±1.16	5.43±0.94	2.33±0.45	2.43±0.40

CSF=cerebrospinal fluid; CC=corpus callosum; SD=standard deviation

Quantitative assessment

There was statistically different in the mean values of clivus/CSF and clivus/CC signal intensity ratio by the grading intensity (Table 2). For clivus/CSF, Grade III showed the highest mean value of clivus/CSF at 5.88 (SD 1.15), compared to Grade II at 4.59 (SD 1.07) and Grade I at 2.95 (SD 0.82). For clivus/CC, Grade III also showed the highest mean value of clivus/CC signal intensity ratio at 2.39 (SD 0.46), compared to Grade II at 1.86 (SD 0.44) and Grade I at 1.15 (SD 0.33).

The mean values of clivus/CSF and clivus/CC signal intensity ratios were increased by ages of both males and females (Table 3). Males had slightly higher mean values in both measurements than females. For instance, the mean values of clivus/CSF and clivus/CC signal intensity ratios in males aged 20 to 29 years were 4.24 (SD 1.08) and 1.66 (SD 0.38), respectively, while the mean values of 4.14 (SD 0.89) and 1.58 (SD 0.34) were identified in females with the same age group.

The difference in the mean values of clivus/CSF signal intensity ratio were larger than the difference in the mean values of clivus/CC signal intensity ratio for all age groups in both unadjusted and adjusted regression analyses (Table 4). Compared to the age of 1 to 9 years, the reference group, the difference in both measurements tended to be larger with increasing ages, but not in the age of 40 to 49 years. After adjustment for gender in the regression model, the difference in the mean values of both measurements were similar to that in unadjusted analysis in terms of magnitude and its direction. For example, in the age group of 20 to 29 years, the mean values of clivus/CSF and clivus/CC signal intensity ratios were 1.28 (95% CI 0.73 to 1.82) and 0.51 (95% CI 0.30 to 0.72) higher compared to the reference group. In the age of 70 to 79 years, the mean values of clivus/CSF and clivus/CC signal intensity ratios were 2.67 (95% CI 2.12 to 3.21) and 1.26 (95% CI 1.06 to 1.47) higher compared to the reference group.

Discussion

Knowledge of marrow transformation is

Table 4. Unadjusted and adjusted analysis for the difference in mean values of clivus/CSF and clivus/CC signal intensity ratio across age groups

Parameters	Clivus/CSF; β (95% CI)		Clivus/CC; β (95% CI)	
	Unadjusted mean difference	Adjusted mean difference*	Unadjusted mean difference	Adjusted mean difference*
Age (years)				
1 to 9	Ref.	Ref.	Ref.	Ref.
10 to 19	1.03 (0.49 to 1.56)	1.05 (0.51 to 1.59)	0.41 (0.21 to 0.62)	0.43 (0.22 to 0.64)
20 to 29	1.27 (0.72 to 1.81)	1.28 (0.73 to 1.82)	0.50 (2.88 to 0.71)	0.51 (0.30 to 0.72)
30 to 39	1.90 (1.36 to 2.45)	1.91 (1.37 to 2.46)	0.80 (0.58 to 1.00)	0.80 (0.59 to 1.01)
40 to 49	1.68 (1.13 to 2.23)	1.69 (1.14 to 2.24)	0.80 (0.58 to 1.00)	0.80 (0.59 to 1.01)
50 to 59	2.11 (1.56 to 2.66)	2.12 (1.57 to 2.67)	0.91 (0.70 to 1.12)	0.92 (0.71 to 1.12)
60 to 69	2.80 (2.25 to 3.34)	2.81 (2.26 to 3.35)	1.21 (1.00 to 1.42)	1.22 (1.01 to 1.42)
70 to 79	2.65 (2.11 to 3.20)	2.67 (2.12 to 3.21)	1.25 (1.04 to 1.16)	1.26 (1.06 to 1.47)

CSF=cerebrospinal fluid; CC=corpus callosum; CI=confidence interval

* Multivariable Gaussian regression model adjusted for sex

important to detect marrow abnormalities on MR images. At birth, the whole skeleton is filled with red bone marrow. The proportion of yellow or fatty marrow increases with age and most of the marrow has undergone conversion by the age of 25 years. Conversion starts from the distal extremities, then progression of the process proximally to the axial skeleton. This normal physiologic marrow conversion follows a predictable pattern throughout the body and within individual bones. Yellow to red marrow reconversion occurs in the exact reverse order, centripetally from the axial to the appendicular skeleton and within the long bones, starting in the proximal metaphysis, followed by the distal metaphysis, and finally within the diaphysis. In times of severe stress, epiphyseal marrow reconversion, marrow cavity expansion, or extramedullary hematopoiesis can occur. Deviation from this pattern suggests an alternative diagnosis[8-11].

The clivus is a bony part of the cranium at the skull base and best seen on the midsagittal MR imaging. The central portion of the clivus is composed of cancellous bone that makes different MR signal characteristics depending on the amount and nature of the marrow elements[1,2]. MR imaging of the brain is one of the most common studies to evaluate the clivus bone marrow, which is best seen on T1-weighted midsagittal cranial image. In this view, other midline structures such as the CC (genu) and the fourth ventricle are also observed on the same plane.

The CC is the largest white matter tract in the brain, connecting the two cerebral hemispheres and providing communication between the cortical and subcortical neurons. The CC is C-shaped in a gentle upwardly convex arch. It is thicker posteriorly and divided into four parts (from anterior to posterior), 1) the rostrum, 2) the genu, 3) the trunk or body, and 4) the splenium. On T1-weighted midsagittal cranial image, the total length (the four parts) of the CC is well visualized. The normal appearance of the CC on MR imaging is similar to those of white matter that show high signal intensity on T1-weighted image[12,13].

For qualitative assessment, the present study showed an association between visual grades of clivus, and gender and age. For quantitative assessment, the mean values of clivus/CSF and clivus/CC signal intensity ratios increased from the visual Grade I to III. The mean values of clivus/CSF signal intensity ratio were greater than that of clivus/CC in all grades, and the values from both measurements increased with ages. The mean value of clivus/CSF signal intensity ratios is greater than the mean value of clivus/CC signal intensity ratio irrespective of age and gender. Males had slightly higher mean signal intensity ratio in both measurements than females. The authors found an association between age and clivus signal intensity ratio using CC as a referent landmark on MR imaging after adjusting the effect of gender in the regression analysis.

Compare to previous studies

The visual grading on clivus bone marrow and age in the authors' study are related, in that Grade I was identified in younger ages, but Grade III was more likely to be identified in older ages. This finding is consistent with previous research where Grade I was not observed after the fifth and sixth decade[4-6,14]. It can be explained that the signal intensity of the clivus bone marrow depends upon mainly hematopoietic cells and fat, and thus the MR signal intensity reflects the ratio of these components. The conversion of red to yellow marrow occurs and corresponds with ages. Fat content in the human bone marrow will give a high signal intensity on T1-weighted MR imaging. However, a report by Okada et al[15] evaluating the relation of marrow conversion in normal subjects under 25 years old showed that Grade I of clivus bone marrow had the highest percentage in the age 0 to 2 years old but was not observed after 6 years old. They proposed that if Grade I was detected in patients aged 3 to 6 years, the presence of infiltrative marrow lesions should be considered. In the present study, however, Grade I was still observed after this age. One of the reasons is that the present study used different classification criteria of visual grading of clivus on MR imaging. The present study used the criteria introduced by Kimura et al[6] that using the percentage of low signal and high signal intensity area in the clivus marrow, whereas the criteria by Okada et al[15] used the homogeneity of clivus signal intensity for grading system. Moreover, the early marrow conversion process in different study populations in terms of ethnicity and gene-environmental factors may play an important role on the discrepancies between the results. Similar to a previous study by Kimura et al[6], the distribution of Grade II was distributed equally in all age categories.

In quantitative assessment, the authors found the mean values of clivus/CSF signal intensity ratio were higher than the mean values of clivus/CC ratio, irrespective of the grades of clivus. Although using different landmarks, the two previous published papers showed the mean values of clivus/CSF signal intensity ratio was higher than that of clivus/pons

when measured on T1-weighted midsagittal cranial image[4,5]. The higher mean values of clivus/CSF were owing to the fact that a signal intensity of CSF was low relative to CC or pons.

Previous studies by Bayramoğlu et al and Olcu et al reported an overall tendency of the mean values of clivus/pons and clivus/CSF signal intensity ratios also increased with ages[4,5]. Bayramoğlu et al[4] reported that the mean values of clivus/pons signal intensity ratio in males were statistically higher than that in females. However, the association of the mean values of clivus/pons signal intensity ratio and ages observed in the previous studies may be confounded by the effect of gender. In the present study, the authors instead used CC as an alternative reference to quantify the signal intensity ratio and acknowledge the effect of gender that might confound the association under study. Thus, the effect of gender is adjusted in the present study analysis. The similar age-related pattern also observed that the mean value of clivus/CSF signal intensity ratio was statistically increased with age. Although in the analysis adjusted for gender, the mean values of clivus/CC signal intensity ratio remained increasing with age. Theoretically, the overall signal intensity of the bone marrow on MR images depends on the ratio of cellular components and fat that has high signal intensity on T1-weighted MR imaging. Hence, the signal intensity ratio reported in the present study corresponds well to the normal physiologic changes of bone marrow with age.

Strength and limitation

The present study has potential strengths. First, the sample in the study was a valid representative for population in the present study settings, since the authors use stratified random sampling by age from the large cohort of individuals that attended MR imaging in the present study radiology department for four years. Therefore, the result can be generalized to Thai population. Second, the MR images were reviewed independently and were given a consensus-based grading by three radiologists. This could yield more accurate in grading of clivus bone marrow. Third, the authors eliminated the effect of gender for assessing the relationship of clivus signal intensity ratio and age. This confirms the age-related pattern of clivus on MR imaging. There are methodological issues that need to be considered. Limited window setting image display chosen for MR imaging of the brain could affect the interpreting of the high signal intensity of clivus. In addition, the exact percentage component of signal intensity in clivus marrow cannot be assessed since the present study using only single T1-weighted midsagittal cranial image to evaluate the visual grading. However, the authors believed that the results remain unchanged, if using another single parasagittal image of clivus.

Implication

In clinical practice, pons is commonly used in normal subjects as reference structure used to compare MR signal intensity of clivus marrow. The present study provides additional information on age-related changes using CC, which is quite similar to the change detected by using pons. It suggests that CC may be a viable alternative reference landmark instead of pons because CC has more homogeneous signal intensity and could be well visualized on T1-weighted midsagittal cranial image. Therefore, CC could be chosen for another reference if the patient had pontine pathology.

Conclusion

There was an association of the mean values of clivus/CC signal intensity ratio and increasing ages. The association is independent of gender. The mean value of clivus to CC signal intensity ratio may be used as an alternative measurement to the mean value of clivus to pons signal intensity ratio in MR imaging of the brain.

What is already known on this topic?

The knowledge on detecting the changes of clivus bone marrow intensity could indicate normal physiology and may raise concerns on abnormalities on MR imaging. The previous reports showed the averages of clivus intensity values that corresponded to age groups by using pons as the reference structure. Although pons is commonly used, some pathologies may be detected especially in elderly patients.

What this study adds?

There was an age-related pattern of clivus bone marrow intensity using CC as a new landmark that showed a similar pattern as of pons. The mean value of clivus to CC signal intensity ratio may be used as an alternative measurement in brain MR imaging.

Conflicts of interest

The authors declare that they have no conflict of interest.

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