Age-Related Changes in Signal Intensity Ratio of Normal Clivus Bone Marrow on Magnetic Resonance Imaging

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ABSTRACT

Objective: To evaluate the association between the signal intensity ratio of clivus bone displayed on magnetic resonance (MR) imaging and ages.

Materials and Methods: A retrospective cohort study of 268 patients underwent brain MR imaging during January 2015 to October 2019. We qualitatively and quantitatively assessed bone marrow signal intensity of clivus bone that were performed on T1-weighted sagittal images. In qualitative assessment, the signal intensities of clivus were visually graded from Grade I to III according to the proportion of low and high signal intensity areas occupying the clival marrow region. In quantitative assessment, we evaluated the association between the signal intensity ratio of clivus to pons and age categorized by decades in multivariable Gaussian regression analysis.

Results: Of 268 patients, the ratio of males to females is 1:1. Grade I clivus was found about 35% of the age 1-9 years, whereas Grade 3 clivus was more frequent (more than 13%) in the ages over 30 years. There were statistically different in the mean values of clivus/CSF and clivus/pons signal intensity ratios by grades. The mean values of clivus/CSF and clivus/pons signal intensity ratios were increased by ages in both sexes, but slightly higher in males. In regression analysis after adjustment for sex, the differences in mean values of clivus/pons signal intensity ratios were larger by increasing age, using the age 1-9 as a reference group.

Conclusion: The present study confirms that signal intensity ratios of clivus to pons on T1-weighted sagittal MR images is increased with ages.

Keywords: Clivus bone marrow; pons; signal intensity ratio; magnetic resonance imaging (Siriraj Med J 2022; 74: 381-387)

Abbreviation

MR : Magnetic resonance
CSF : Cerebrospinal fluid
ROI : Region-of-interest
SD : Standard deviation.

INTRODUCTION

The clivus is located centrally between foramen magnum and dorsum sellae of the skull base and clearly seen on T1–weighted sagittal MR images of the brain. It is an important site for evaluating bone marrow signal intensity.[1-4] Using magnetic resonance (MR) imaging has shown advantages in wide range of radiologic research including to detect of disease severity[5], to grade/stage pathologic conditions[6] and to assess bone structures and its components, for instance. Since MR is a sensitive and

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http://dx.doi.org/10.33192/Smj.2022.46

noninvasive tool, it is superior to other devices used for evaluating bone marrow and detecting pathologic changes. The device can differentiate fat from other tissues on T1-weighted images without contrast-enhanced materials. On MR imaging, the yellow marrow has a high signal intensity, whereas the red marrow has almost an intermediate signal intensity. Previous research showed that the signal intensity of the marrow on T1-weighted images can be used to detect age-related changes of the clivus bone in normal people, in that the value was increased with age which reflect the change from red to yellow marrow.[7–10]

Alteration of the signal patterns of clivus bone marrow on MR imaging should be assessed because the information may indicate whether bone maturation completely corresponds with age and it suggests marrow abnormalities before morphologic bone changes. Often, age-related abnormalities of bone marrow signal intensity is the only sign of bone diseases detected on MR imaging. Although many previous studies have shown that the signal intensity of clivus bone is associated with age, all studies were mainly conducted in non-Asian population, and did not take confounding factors into account.[1,2]

Therefore, the purpose of this study was to qualitatively and quantitatively evaluate of bone marrow signal intensity of clivus bone and to assess whether clivus bone marrow signal intensity on MR images is related to age.

MATERIALS AND METHODS

This was a retrospective study that was approved by the institutional ethics committee and did not require informed consent.

From January 2015 to October 2019, the medical records were examined. The study comprised patients who had had brain MR imaging at Naresuan University's Radiology department in Phitsanulok, Thailand. Patients who were (1) younger than 1 year old due to immature myelination, (2) older than 79 years old due to aging brain or abnormal brain imaging such as abnormalities of clivus and pons structure, and (3) diagnosed with known diseases involving the skull base, as well as those who had systemic diseases such as hematopoietic diseases, lymphoproliferative disorder, and hematogenous metastases or had previous radiation therapy, chemotherapy, or intracranial surgery, were excluded. We used stratified random sampling to divide the age groups into decade groups (i.e., 1-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, and 70-79 years). Each age category had a sample size of around 30% of the original age categories. The MR appearance of clivus on T1-weighted sagittal images was studied in a total of qualified 268 patients.

Imaging procedures

A 1.5-T MR scanner (Philips Ingenia, Philips Medical Systems, Best, the Netherlands) was used for all MR exams. Standard spin-echo T1-weighted midsagittal images (TR = 550 msec, TE = 15 msec, 5 mm section thickness, 200 mm field-of-view, number of signal acquisitions = 1, and a 196x196 matrix size) were used as part of the imaging technique. For this study, T1-weighted midsagittal cranial images were used. Midline features such as the clivus, pons, and fourth ventricle are seen on the same plane in this image. In individuals without disease involving the brain, the pons and the cerebrospinal fluid (CSF) were chosen as reference landmarks with stable MR signal intensity values. Three radiologists (W.G., N.O., S.T.) were blinded to the information connected to the images, such as the patients' name, age, and gender, and examined both qualitative and quantitative MR imaging assessments.

Assessments of clivus signal intensities

The signal intensities of clival bone marrow were visually rated from Grade I to III based on the proportion of low and high signal intensity areas inhabiting the clival marrow region for the qualitative assessment. This grading system was previously utilized by Kimura et al.[3] Grade I denotes a predominantly low signal intensity, occupying more than 50% of the clivus, Grade II denotes a low-signal-intensity portion occupying less than 50% but greater than 20% of the clivus, and Grade III denotes a predominantly high signal intensity, with some low signal intensities, occupying less than 50% but greater than 20% of the clivus (Fig 1). We arrived at a grading that was agreed upon by three radiologists. When there was a disagreement between radiologists' readings, the consensus-based debate was held.

The signal intensity values for the area of interest (ROI) in the clivus, pons, CSF, and background noise were employed for the quantitative assessment. The signal intensity values measured from the clivus, pons, and CSF were subtracted from the background noise represented by air next to the vertex at a level comparable to the clivus. The circular ROI was placed and verified by one of our radiologist team (N.O.). The three main locations of ROI were specified at the center of clivus, pons, and the fourth ventricle. The size of the area to be measured was set to 0.10 cm^2 to prevent including the cortical bone in the ROI (Fig 2). The signal intensity ratios of (1) clivus to CSF (clivus/CSF) and (2) clivus to pons (clivus/pons) were calculated using this data.

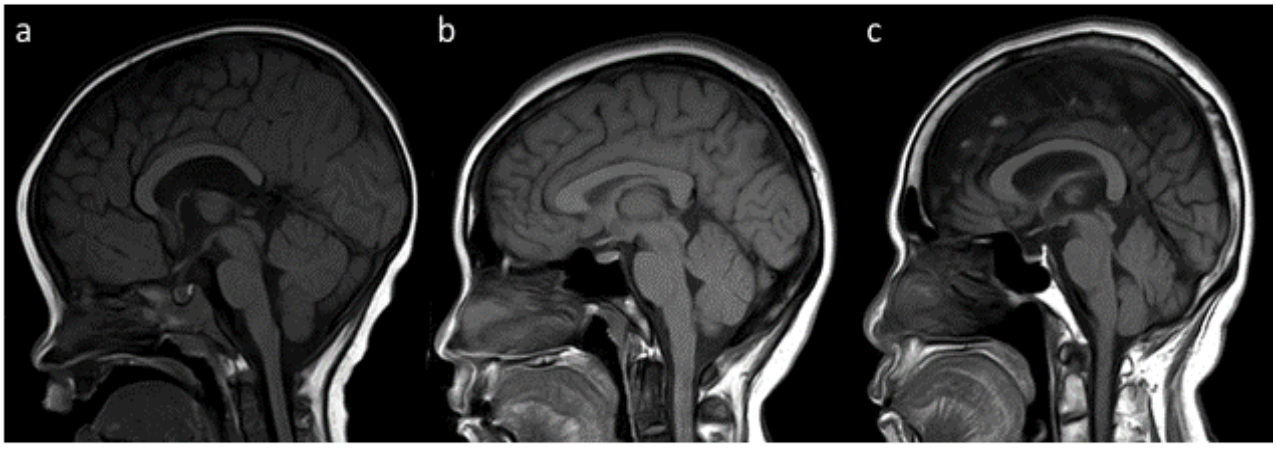

Fig 1. Midsagittal T1-weighted MR imaging of normal clivus bone marrow on qualitative assessment. (a) Grade I in 1-year-old boy (b) Grade II in a 32-year-old female (c) Grade III in a 75-year-old female.

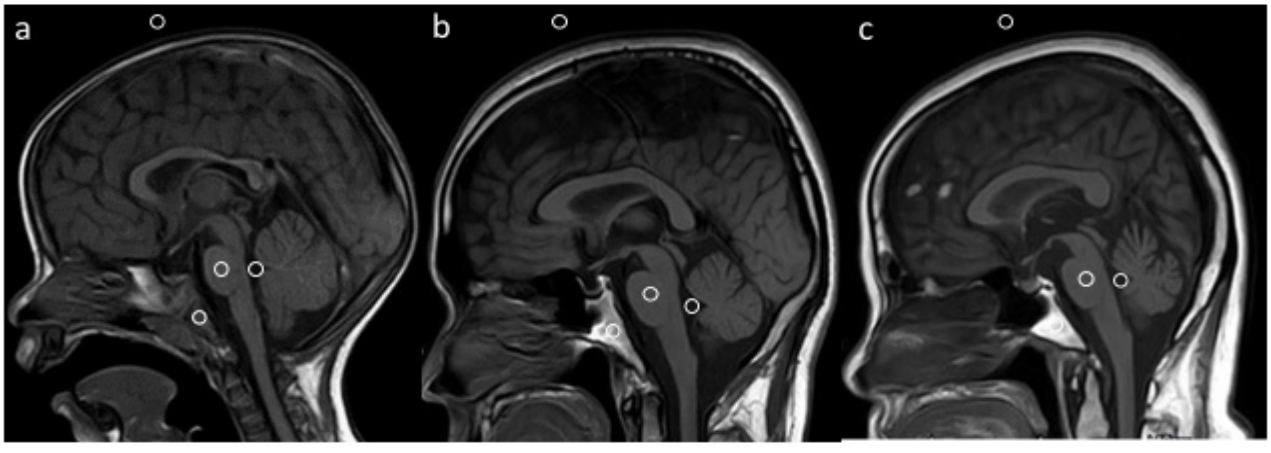

Fig 2. Midsagittal T1-weighted MR imaging of normal clivus bone marrow on quantitative assessment, measured by placing the white circle at the region of interest (clivus, pons, CSF, and the background noise). (a) In a 1-year-old girl (b) In a 46-year-old male (c) In a 75-year-old female.

Statistical analysis

Descriptive statistics for categorical variables were presented in the form of frequencies and proportions. Mean and standard deviation (SD) were used to summarize continuous variables. Using one-way ANOVA with equal variances, we compared the mean values of clivus/CSF and clivus/pons signal intensity ratios by grading intensity. Barrett's test was used to determine the equality of the variances. The relationship between the mean values of clivus/pons signal intensity ratios and age groups was investigated using multivariable Gaussian regression analysis. In the regression analyses, the age group of 1 to 9 years was chosen as the reference category. The difference in the mean values of signal intensity ratios was represented by the beta-coefficients (β) from the regression model. Stata version 12.1 and R Studio version 4.0.2 were used for all statistical analyses. The significance level (α) was set at < 0.05.

All brain imaging were checked and reviewed by three radiologists. We reported a good inter-observer agreement on MRI reading in our previous research.[9]

RESULTS

Table 1 showed the distribution of sex and age of the study patients by the MR signal intensity grading of normal clivus bone marrow. The percentage of Grade I decreased with increasing ages, and particularly was found less than 10% in age groups over 40 years. The highest percentage was found at the first decade (approximate 36%). Grade I was not found in patients over the age of 70. In contrast, the percentage of Grade III increased with age and was more frequent than 10% in each age group over the age of 30 where the highest proportion (27.9%, n=17) was at the age of 60-69. At the first decade, Grade III was not found. Over the age of 40, Grade I and Grade III became more different in proportions. There

TABLE 1. Distributions of sex and age by the Graded MR Signal Intensities of Normal Clivus Bone Marrow.

	Total (N=268)	Grade I (n=45) n (%)	Grade II (n=162) n (%)	Grade III (n=61) n (%)
Sex				
Female	132	24 (53.3)	82 (50.6)	26 (42.6)
Male	136	21 (46.7)	80 (49.4)	35 (57.4)
Age (years)				
1-9	33	16 (35.6)	17 (10.5)	0 (0)
10-19	31	8 (17.8)	19 (11.7)	4 (6.6)
20-29	30	5 (11.1)	22 (13.6)	3 (4.9)
30-39	36	6 (13.3)	19 (11.7)	11 (18.0)
40-49	36	4 (8.9)	24 (14.8)	8 (13.1)
50-59	36	4 (8.9)	22 (13.6)	10 (16.4)
60-69	36	2 (4.4)	17 (10.5)	17 (27.9)
70-79	30	0 (0)	22 (13.6)	8 (13.1)

were different in proportion between males to females in Grade I (46.7% and 53.3%) and Grade III (57.4% and 42.6%) was different, whereas the proportion of males to females in Grade II was nearly equal.

Table 2 showed the mean values of clivus/CSF and clivus/pons signal intensity ratio by grading. The mean values of clivus/CSF measured in Grade I to III were 2.99 (SD= 0.83), 4.60 (SD=1.05), and 5.89 (SD=1.08) respectively. There were statistically significant (P< 0.001) of the mean values between the grades. The mean values of clivus/pons signal intensity ratios also increased by the respective grades. The mean values of clivus/pons measured in Grade I to III were 1.22 (SD= 0.32), 1.94 (SD=0.41), and 2.47 (SD=0.43) respectively, and were statistically different (P< 0.001). The mean values of clivus/CSF signal intensity ratio were higher than clivus/pons in all grades.

Table 3 showed the mean values of clivus/CSF and clivus/pons signal intensity ratios stratified by sex. The mean values of clivus/CSF and clivus/pons signal intensity ratios increased with age in both males and females. Males had slightly higher mean values in both measurements than females in all age groups. Irrespective to sex, the mean values of clivus/CSF were higher than clivus/pons in all age groups. For example, the mean values of clivus/CSF and clivus/pons signal intensity ratios were 5.12 (SD=1.06) and 2.13 (SD=0.40) in males aged 30-39 years, and the respective mean values were 4.54 (SD=1.00) and 1.86 (SD=0.44) in females in the same age group.

TABLE 2. Descriptive Values of clivus/CSF and clivus/pons Intensity Ratios in All Individuals According to the Grades.

	Grade I (n = 45) Mean ± SD	Grade II (n=162) Mean ± SD	Grade III (n=61) Mean ± SD	P-value
clivus/CSF	2.99 ± 0.83	4.60 ± 1.05	5.89 ± 1.08	<0.001*
clivus/pons	1.22 ± 0.32	1.94 ± 0.41	2.47 ± 0.43	<0.001*

* One-way ANOVA with equal variances

TABLE 3. Descriptive Values of clivus/CSF and clivus/pons Intensity Ratios Comparatively for Each Age Group in Males and Females.

Age groups	clivus/CSF, Mean ± SD		clivus/pons, Mean ± SD	
	Female, (n =132)	Male, (n = 136)	Female, (n = 132)	Male, (n =136)
1-9	2.65 ± 0.58	3.13 ± 0.72	1.12 ± 0.29	1.28 ± 0.30
10-19	3.89 ± 1.10	4.03 ± 1.13	1.59 ± 0.41	1.63 ± 0.46
20-29	4.14 ± 0.89	4.24 ± 1.08	1.66 ± 0.34	1.74 ± 0.39
30-39	4.54 ± 1.00	5.12 ± 1.06	1.86 ± 0.44	2.13 ± 0.40
40-49	4.53 ± 1.34	4.71 ± 0.99	1.89 ± 0.43	2.05 ± 0.47
50-59	5.19 ± 1.06	4.81 ± 1.17	2.18 ± 0.43	2.06 ± 0.42
60-69	5.68 ± 1.08	5.84 ± 1.41	2.39 ± 0.41	2.44 ± 0.59
70-79	5.72 ± 1.16	5.43 ± 0.94	2.41 ± 0.41	2.36 ± 0.36

In crude analysis, there were statistically differences in the mean values of clivus/CSF and clivus/pons signal intensity ratios increasing with age groups, using the age of 1-9 years as the reference group. For example, the mean values of clivus/CSF signal intensity ratios at age 30-39 years was 1.91 (95%CI: 1.40, 2.41) and clivus/pons was 0.78 (95% CI: 0.58, 0.97) higher than that of the reference group. After adjustment for sex in the regression analysis, the beta-coefficients were similar in terms of magnitude and its direction to the crude analysis. For example, the mean values of clivus/CSF and clivus/pons signal intensity ratios at age 30-39 years were 1.91 (95%CI: 1.41, 2.42) and 0.78 (95%CI: 0.58, 0.98) higher compared to the reference group (Table 4).

TABLE 4. Crude and adjusted analysis for the differences in mean ratio of clivus/CSF and clivus/pons across age groups.

Parameters	clivus/CSF		clivus/pons	
	Crude Mean Difference, β (95%CI)	Adjusted Mean Difference*, β (95%CI)	Crude Mean Difference, β (95%CI)	Adjusted Mean Difference*, β (95%CI)
Age (years)				
1-9	Ref	Ref	Ref	Ref
10-19	1.03 (0.51, 1.56)	1.05 (0.52, 1.58)	0.40 (0.19, 0.60)	0.41 (0.19, 0.61)
20-29	1.27 (0.73, 1.80)	1.28 (0.74, 1.81)	0.48 (0.27, 0.68)	0.49 (0.28, 0.69)
30-39	1.91 (1.40, 2.41)	1.91 (1.41, 2.42)	0.78 (0.58, 0.97)	0.78 (0.58, 0.98)
40-49	1.68 (1.17, 2.19)	1.70 (1.19, 2.21)	0.75 (0.54, 0.94)	0.76 (0.56, 0.95)
50-59	2.06 (1.55, 2.57)	2.07 (1.55, 2.57)	0.90 (0.70, 1.09)	0.90 (0.71, 1.10)
60-69	2.84 (2.33, 3.35)	2.85 (2.34, 3.36)	1.20 (1.00, 1.40)	1.20 (1.00, 1.40)
70-79	2.65 (2.12, 3.18)	2.66 (2.13, 3.19)	1.17 (0.96, 1.37)	1.17 (0.96, 1.38)

* Multivariable linear regression model adjusted for sex

DISCUSSION

Normal marrow conversion process represents the gradual replacement of red marrow to yellow marrow. During infancy period, red marrow is predominant in both appendicular and axial skeletons and has converted to yellow marrow by the time. In adults approximately 25 years old, the red marrow residuals remain in the axial skeletons.[7–10,12–15]

Red marrow consists of 40% fat, 40% water and 20% protein, whereas yellow marrow consists of approximately 80% fat, 10–15% water, and 5% protein.[7,8,12–14] MR imaging is superior to other imaging devices to detect bone marrow conversion and related diseases. On T1-weighted images, yellow marrow has a high signal intensity, while red marrow has intermediate signal intensity.[2,4,8]

The clivus is an important site to evaluate bone marrow abnormalities because it is located centrally in the skull base and can be seen on routine sagittal T1–weighted MR images.[1,3]

The present study showed that, in the qualitative assessment of clivus, Grade I was more observed in young ages, whereas Grade III was more in old ages. In the quantitative assessment, the mean values of clivus/CSF and clivus/pons signal intensity ratios were increased with age in both female and male. The mean values of signal intensity ratios of both measurements in males were slightly higher than females. After adjustment for sex in the regression analysis, the mean values of clivus/CSF and clivus/pons signal intensity ratios remained the same and slightly higher than unadjusted analysis in some age groups, but the differences in mean values were also increased with age. The mean values of clivus/CSF were greater than that of clivus/pons irrespective of age.

Comparison to previous studies

In the qualitative assessment, the distribution of sex and age by the visual gradings (Grade I to III) of MR imaging clivus observed in our study was consistent with previous research.[1,3,16] A study by Okada et al.[17] evaluating the relation of marrow conversion with ages in normal patients under 25 years old showed that Grade I was more frequently observed in the age of 0-2 years old, whereas Grade III was more observed in the older ages. Grade I was not observed after the age of 6 years old. From this study, it may imply that abnormal infiltrative marrow lesions should be concerned when Grade I was detected after this age. In our study, however, we still observed Grade I after the age of 6. The discrepancy may be because of the difference in the classification criteria of the visual grading of clivus on MR imaging. The previous study used the criteria that is more subjective to grade clivus bone (Grade I = uniformly low signal intensity, relatively isointense to muscle, Grade II = mixed low and high signal intensity portion, and Grade III = almost uniformly high signal intensity, relatively isointense to subcutaneous fat) than the criteria used in our study. We estimated the percentage of the components of bone marrow signal intensity according to a study by Kimura et al.[3] (Grade I = predominantly low signal intensity, occupying more than 50% of the clivus; Grade II = low-signal-intensity portion occupying less than 50% but greater than 20% of clivus; Grade III = predominantly high signal intensity, occupying less than 20% of the clivus). In addition, the early marrow conversion process may be different across study populations in terms of genetic and environmental factors which contribute to the discrepancies between studies.

In quantitative assessment, our findings were also consistent with previous studies[1,2] that showed the age-related pattern of the mean values of clivus/pons signal intensity ratios. The pattern can be explained by the physiologic change of normal marrow conversion as it was detected from signal intensity on T1-weighted images. A study by Bayramglu et al.[2] reported that the mean value of clivus/pons signal intensity ratio in males was slightly higher than that in females. However, this information indicates that the association of the mean values of clivus/pons signal intensity ratio and ages observed in this study may be confounded by sex. In our study, the association of the mean values of clivus/pons signal intensity ratio and ages remained unchanged although the effect of sex was adjusted in the regression analysis. Thus our findings confirmed that there is an association between the mean values of clivus/pons signal intensity ratio and ages. In all studies, the mean value of clivus/CSF signal intensity ratio was higher than that of clivus/pons. It is due to the fact that the signal intensity of CSF was lower than pons that yield the lower ratio of clivus/pons relative to clivus/CSF. In addition to statistical significance of age-related change of clivus in our study, both clivus/pons and clivus/CSF signal intensity ratio have shown clinical implication in practice since the homogeneous property of pons is a good landmark to provide more details on sagittal T1–weighted MR images of the brain. Although clivus/CSF does not much carry potential information, it is needed to be estimated as to evaluate the abnormalities of clivus.

Strengths and limitations

Our research has some potential strengths. First, the

sample for our study was derived by stratified random sampling by age from a large cohort of subjects who had undergone MR imaging and had no abnormalities of the clivus bone marrow in our radiology department over a four-year period. This sample was a good representation of the general population in our settings. As a result, our findings can be generalized to Thai population. Second, three radiologists independently assessed the MR imaging. In the event of disagreement, the values of MR imaging measures and visual grading of the clivus bone were determined by consensus. This may lead to more precise grading of clivus bone marrow. Third, the effect of gender on the association between clivus signal intensity ratios and age was excluded. Our present study confirms the age-related change of clivus on MR imaging. However, some methodological concerns must be addressed. The interpretation of the high signal intensity from clivus could be hampered by the limited window setting image presentation used for MR imaging of the brain. Furthermore, because we only employed a single T1-weighted midsagittal cranial image to evaluate the visual grading, we were unable to determine the precise percentage component of signal intensity in clivus marrow. However, we assume the results will be the same if we use another single clivus parasagittal image.

Implication to clinical practice

The present study suggested that the signal intensity of clivus bone Grade I should not be detected on T1-weighted of brain MR imaging in the old ages. If it is present, abnormal infiltrative marrow lesions could not be excluded. In addition, the signal intensity ratio of clivus bone marrow is a good indicator to evaluate the abnormalities of bone marrow since the value is related to ages.

CONCLUSION

The present study confirms that there is an association of signal intensity of clivus to pons ratio and age where the relationship is independent of gender.

ACKNOWLEDGEMENTS

We gratefully acknowledge the hard work, efficiency, and devotion of our imaging technicians, which made this work possible.

Funding: This article was financially supported by Faculty of Medicine, Naresuan University.

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