Effects of Age, Gender and Hemispheric Location on T2 Hypointensity in the Pulvinar at 3T

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Key words: MR imaging, pulvinar, T2 hypointensity

SUMMARY – *Pulvinar signal intensity decrease on T2-weighted images has been reported in some neurological abnormalities. We aimed to define the normal T2 signal hypointensity pattern present in the pulvinar to avoid erroneous radiological interpretation. One hundred and forty-two subjects (54 men and 88 women; age range 9-91 years) with unremarkable brain 3T MR findings were enrolled. MR images were analyzed with regard to signal intensity of the pulvinar relative to the thalamus on fluid attenuated inversion recovery images. Effects of age, gender and hemispheric location on the degree of T2 hypointensity were statistically analyzed. The statistical association was measured between the pattern of signal changes in the pulvinar region and that in the putamen and the globus pallidus. We detected a linear signal decrease in the pulvinar region with age. The male subjects had a more rapid decrease of signal with age than female subjects. The right pulvinar region had a higher chance of hypointensity compared to the left. A positive linear association was found when signal change from the pulvinar region was compared with signal in the putamen and globus pallidus. We detected a linear signal decrease with age in the pulvinar. The physiological signal features of the pulvinar also depend on gender and hemispheric lateralization. The pattern of signal change in the pulvinar is similar to but not the same as that in the putamen and globus pallidus.*

Introduction

Bilateral pulvinar signal intensity decrease on T2-weighted images has been reported in aspartylglucosaminuria¹. Patients with Fabry disease also have been found to have slightly decreased pulvinar signal intensity on T2-weighted images^{2,3}. Recently a number of reports have been published describing signal loss in the pulvinar with susceptibility weighted images utilizing phase and magnitude data in subjects with multiple sclerosis (MS), multiple system atrophy with predominant parkinsonism (MSA-P) and idiopathic Parkinson disease (IPD)⁴⁻⁸. In our routine practice, however, fluid attenuated inversion recovery (FLAIR) images of the brain at 3T frequently show hypointensity in the most posterior region of the thalamus that is equivalent to the pulvinar region.

This is in subjects with no reported pulvinar dysfunction or pathological condition affecting the pulvinar. This hypointensity has at times created diagnostic uncertainty. In particular, pulvinar signal hypointensity on FLAIR has been a point of discussion in MS patients or when detected in an older patient as to whether it is a sign of neurodegeneration⁹⁻¹². Therefore, it is important to understand normal signal appearances of the pulvinar so that the physiological features are not confused with pathological changes. It is particularly important to understand the signal intensity changes on T2 FLAIR since it is a standard sequence used extensively for evaluating the brain.

A review of the literature suggests that pulvinar hypointensity may be related to iron deposition. Previous studies have shown in a limited fashion that the pulvinar regions in

Figure 1 Axial fluid attenuated inversion recovery image. A) Note the hypointensity of the bilateral pulvinar regions (arrows). B). Regions of interest represent measurements made in the hypointense pulvinar region (1 and 2), central thalamus (3 and 4), putamen (5 and 6), and globus pallidus (7 and 8).

normal brains were stained by Perls' stain for ferric iron, but the iron deposition was not discussed^{13,14}. If the T2 hypointensity in the pulvinar region is caused by iron deposition, it may appear in normal brains with some regular patterns rather than randomly. Studies have reported iron-related signal loss on T2-weighted imaging in the putamen, globus pallidus, red nucleus, substantia nigra, and dentate nucleus¹⁵⁻¹⁷. However, T2 signal changes in the pulvinar thalamus have not been described. It is very likely because these studies were at 1.5T and also FLAIR imaging was not evaluated. Brain iron deposition increases with the normal aging processes, and T2 signal intensity in the deep gray matter decreases in an inverse proportion to age¹⁵⁻¹⁷. In addition, there may be gender-related differences in iron deposition. Bartzokis et al. reported that women have significantly lower ferritin iron than men in some deep gray and white matter¹⁸. Also, the potential effect of iron deposition may have asymmetric hemispheric localization. Xu et al. found a leftward bias of iron content in the brain¹⁹. To our knowledge, only one study has evalu-

ated the putative iron content in the pulvinar thalamus of healthy adults using susceptibility weighted imaging phase and T2* weighted magnitude values. In this study iron concentration was found to increase linearly with age²⁰.

We hypothesized that T2 hypointensity is age, gender, and hemisphere-related. There may also be a similarity in the signal changes between the pulvinar and the putamen or globus pallidus if the reason for the hypointensity is iron deposition. The purpose of this study was to define the normal T2 signal hypointensity pattern present in the pulvinar to avoid erroneous radiological interpretation with FLAIR imaging.

Materials and Methods

Subjects

We searched the medical records and imaging database from our institution for subjects with unremarkable brain 3T MR findings. In all, 142 consecutive subjects (54 men, aged 9-

82 years [mean, 43.9 years] and 88 women, aged 8-91 years [mean, 45.2 years]) that met the study criteria were identified and enrolled in this retrospective study. Each subject's MR imaging was interpreted as having normal brain findings with the exception of some elderly subjects whose MR images showed mild small vessel ischemic findings in the white matter and/or mild to moderate cerebral atrophy. The subjects with small vessel ischemic findings and lacunar infarcts in the thalamus were not included. The medical records were reviewed and subjects with neurodegenerative diseases, iron deposition diseases, MS, or other final diagnosis reflective of neurocognition disorders or dysfunction were excluded. Institutional review board approval was obtained, and informed patient consent was not required for the retrospective review of the medical records or the evaluation of the MR images for this HIPAA-compliant study.

MR imaging

MR imaging was performed on a 3T MR imaging unit (Signa HDx; GE Healthcare, Milwaukee, WI, USA) with an eight-channel head coil. All subjects underwent axial FLAIR imaging with TR/TE/TI of 9500/120-130/2250; matrix of 325×224 , field of view of 22×22 , section thickness of 5 mm, section gap of 1 mm, and NEX of 1.

Imaging processing

The FLAIR images of these subjects were analyzed on a workstation (ADW 4.3, GE Healthcare). Two authors (M.L.W. and Y.Z.) reached a consensus regarding the presence or absence of hypointensity in the pulvinar region in the most posterior region of the thalamus. We measured the signal intensity of the pulvinar region showing the hypointensity. Slice selection for measurement was determined using the slice showing the largest portion of the pulvinar region. In subjects without a hypointense pulvinar on FLAIR, the signal intensity was measured in the center of the most posterior region of the thalamus.

The signal intensity was also measured in the putamen, globus pallidus, and center of the thalamus on the same slice. One author (Y.Z.) blinded to the subjects' age and gender manually traced the ROIs for the measurement. The ROIs drawn were as large as possible on the hypointensity area in the pulvinar region,

putamen, and globus pallidus without risking partial volume effects with the edge. The ROIs on the center of the thalamus was approximately 40 mm² (Figure 1).

The pulvinar hypointensities were compared on the basis of age, gender and hemispheric differences. We also calculated the signal ratios to evaluate effects of age, gender and hemispheric location on the signal changes in the pulvinar regions, putamen and globus pallidus. The signal intensity of the center of the thalamus was used as a reference. The calculation formulas were Spv/St, Spt/St, and Sgp/St. Spv, Spt, Sgp, and St are the average signal intensity of the ROI in the pulvinar regions, putamen, globus pallidus, and thalamus, respectively. In addition, the signal ratios of the pulvinar regions were compared with those of the putamen and globus pallidus to analyze the similarity of the signal changes.

Statistical analysis

Data analysis was performed by a biostatistician (FY) using commercial statistical software, SAS, Version 9.2 (SAS Institute, Cary, NC, USA). The generalized estimating equation (GEE) model with logit link for binomial distributed data was modeled on the hypointensity detection to compare the chance of having hypointensity in pulvinar between different genders, hemispheric locations and age groups.

The mixed effects model was respectively fit on each signal ratio to evaluate the age, gender and hemispheric location effects, adjusting for the correlation of observations within the same subject. The interaction between age and sex was included in all models as they are statistically significant ($p < 0.05$). The significant interaction between age and sex implies that the age effects on the signal ratio were different between genders. We also fit the mixed model separately for males and females to estimate the hemispheric location adjusted age effects for males or females.

The mixed effects model was also fit to investigate the age, sex and hemispheric location adjusted linear association of the signal ratio in the pulvinar region with the signal ratios in the putamen and globus pallidus simultaneously.

All mixed effects models include the signal from thalamus as a covariate to eliminate the indirect effects from different sized denominators in ratio regression fitting the signal ratio outcome variables²¹.

Figure 2 Graph shows that the negative age effect on signal ratio of the pulvinar in the males (estimated coefficient = -0.0029 , 95% confidence interval = $-0.0035 \sim -0.0023$, $p < 0.0001$) is larger than that in the females (estimated coefficient = -0.001 , 95% confidence interval = $-0.0016 \sim -0.0004$, $p < 0.001$).

Figure 3 Graph shows that the negative age effect on signal ratios of the putamen in the males (estimated coefficient = -0.005 , 95% confidence interval = $-0.0056 \sim -0.0046$, $p < 0.0001$) is larger than that in the females (estimated coefficient = -0.003 , 95% confidence interval = $-0.0035 \sim -0.0024$, $p < 0.0001$).

Figure 4 Graph shows that the negative age effect on the signal ratios of the globus pallidus in the males (coefficient estimate = -0.0024 , 95% confidence interval = $-0.0030 \sim -0.0018$, $p < 0.0001$) is larger than that in the females (coefficient estimate = -0.0015 , 95% confidence interval = $-0.0020 \sim -0.0010$, $p < 0.0001$).

Results

Detection of T2 hypointensity in the pulvinar regions

Among the 142 subjects, 107 had hypointensity on FLAIR imaging in the pulvinar region bilaterally. Seven subjects had hypointensity only in the right pulvinar region. No hypointensity was found only in the left pulvinar re-

gion. Detection of the hypointensity based on age, gender and hemispheric location is summarized in Table 1.

The results from the GEE model imply the right side of the pulvinar region has a higher chance of hypointensity compared to the left side with an odds ratio (OR) = 1.5 and 95% confidence interval (CI) for OR = (1.1, 2.0). Subjects younger than 20 years old have the lowest chance of hypointensity ($p < 0.001$). Spe-

cifically, compared to the subjects of age 20 or younger, the subjects age 21-40 years have a 13 times higher odds (95% CI: 3.3, 58.6) of having hypointensity, the subjects age 41 to 60 years have a 39 times higher odds (95% CI: 9.4, 170.2), while the subjects age 61 years or older have 28.5 times higher odds (95% CI =5.9, 147.3) of having hypointensity. No significant difference exists for the chance of hypointensity between males and females.

Signal ratios

The signal intensity was measured in the pulvinar regions that showed hypointensity on FLAIR imaging. The signal ratios relative to the center of the thalamus were calculated. In addition, the signal ratios of putamen and globus pallidus relative to the center of the thalamus were also calculated in the same subjects. The values of ratio are summarized in Table 2.

Effects of age, gender, and hemispheric location on T2 signal changes

The signal ratios measured from the pulvinar region, putamen, and globus pallidus significantly decreased in inverse proportion to the age in both male and female subjects. The estimated age coefficients and their 95% con-

fidence interval, which were calculated based on evaluating the signal change with age increasing by one year after adjusting for hemispheric location effects, quantitatively showed the detailed differences between male and female subjects (Figures 2 to 4). The significant interaction between age and sex was found in all three ratios: the pulvinar region ($p < 0.001$), putamen ($p < 0.001$), and the globus pallidus ($p = 0.01$), implying that the negative age effect on signal ratios in the males was larger than that in the females. The signal ratio from the left side was higher than that from the right side in the pulvinar region ($p = 0.001$). However, in the globus pallidus, the higher signal ratio was found in the right side ($p = 0.04$). No difference was observed in the ratio of putamen between left and right sides of the same person.

Association between T2 signal changes in pulvinar and putamen or globus pallidus

There were positive linear associations between the signal ratios from the pulvinar region and the putamen ($p < 0.0001$) and the globus pallidus ($p < 0.0001$). The linear coefficient of the signal ratio of the putamen is 0.43, while the coefficient of the signal ratio of globus pallidus is 0.25. It is expected that the difference

Table 1 Hypointensity in the pulvinar region based on age, gender, and hemispheric location.

Gender	Hemisphere	Age				Total (n=142; M=54, F= 88)
		≤20 y/o * (n=17; M=10, F=7)	21-40 y/o (n=42; M=12, F=30)	41-60 y/o (n=54; M=20, F=34)	≥61 y/o (n=29; M=12, F=17)	
M (n=54)	Right	1 (10%)	9 (75%)	20 (100%)	11 (91.7%)	41 (75.9%)
	Left	1 (10%)	8 (66.7%)	20 (100%)	11 (91.7%)	40 (74.1%)
F (n=88)	Right	3 (42.9%)	25 (83.3%)	30 (88.2%)	15 (88.2%)	73 (83%)
	Left	2 (28.6%)	23 (76.7%)	28 (82.4%)	14 (82.4%)	67 (76.1%)

Data are numbers and percentages of subjects with hypointensity in the pulvinar region. *: The youngest subject with a detectable T2 hypointensity was 18 years old.

Table 2 Signal ratios of the pulvinar, putamen, and globus pallidus to the central thalamus.

		Signal Ratios (mean ± S.D.)
Pulvinar	Right	0.69 ~ 1.04 (0.89 ± 0.07)
	Left	0.70 ~ 1.04 (0.92 ± 0.07)
Putamen	Right	0.63 ~ 1.22 (0.90 ± 0.10)
	Left	0.64 ~ 1.12 (0.90 ± 0.10)
Globus Pallidus	Right	0.52 ~ 0.97 (0.70 ± 0.07)
	Left	0.47 ~ 0.95 (0.68 ± 0.07)

Figure 5 Graph shows the positive linear association between the ratios from the putamen and the pulvinar region ($P < 0.0001$) adjusting for the confounding effects of thalamus signal, side, age, sex, and signal ratio from globus pallidus.

Figure 6 Graph shows the positive linear association between the ratios from the globus pallidus and the pulvinar region ($P < 0.0001$) adjusting for the confounding effects of thalamus signal, side, age, sex, and signal ratio from putamen.

in the signal ratios of the pulvinar region is 0.43 associated with one unit difference in the signal ratio of putamen (Figure 5) and is 0.25 associated with one unit difference in the ratio of the globus pallidus (Figure 6).

Discussion

Our study evaluated and confirmed a significant association between the pulvinar signal on FLAIR and age (Table 1). The analysis of the signal ratio of the pulvinar region versus the thalamus showed a significantly negative age effect (Figure 2) which also suggests the signal decreases in the pulvinar are secondary to the aging processes. The youngest subject with detectable T2 hypointensity was 18 years old. Although it is hard to draw a definite conclusion with the small number of subjects in our study, obvious pulvinar T2 hypointensity may not appear in childhood and adolescence. This is different from the signal changes in the globus pallidus. Aoki et al. reported that the globus pallidus begins to show obvious hypointensity in the 11-15-year age range¹⁵.

From Figure 2 it can be seen that the pulvinar signal ratios in some subjects who were more than 60 years old were not lower than in younger subjects. This suggests that the signal decreases more slowly or even stops in some

subjects after age 60 years. Based on the previous studies, iron content reaches a maximum level during the 5th decade in structures such as the putamen and caudate nucleus^{20,22}. Similar changes in iron level may occur in the pulvinar region. In addition, subtle signal changes in the normal-appearing pulvinar region and thalamus caused by small vessel ischemia in older subjects could affect the signal changes. Any increase in water content may hide an R2 (longitudinal relaxation rate equal to the reciprocal of T2 relaxation time ($R2 = 1/T2$)) effect and this may obscure the pulvinar hypointensity we are measuring²⁰.

The negative age effect on the signal ratio in the males was significantly larger than that in females (Figure 2), indicating the signal decreases more in the pulvinar region in males than in females of the same age. In addition, we found more of a propensity of subjects having greater hypointensity in elderly males than in elderly females (Table 1). Bartzokis et al. evaluated gender differences in brain iron level utilizing the field-dependent relaxation rate increase method. Their data showed that men have significantly higher iron than women in the caudate, thalamus, frontal white matter, and corpus callosum¹⁸. This would explain our findings of gender-related hypointensity differences in the pulvinar region. However, by using susceptibility-weighted imaging, Xu et al. reported

that there are no gender differences in the iron content of the basal ganglia, substantia nigra, red nucleus, and frontal white matter¹⁹. The inconsistency of these two previous studies could mainly be attributed to the differences in the MR techniques applied or could be due to differences in the populations analyzed. Further studies with more cases are needed to confirm the gender-related difference in brain iron levels.

The female subjects 20 years old or younger in this study had a higher incidence of hypointensity in the pulvinar region than the male subjects of the same age (Table 1). This is contrary to the result in the subjects who were more than 40 years old. However, only ten males and seven females 20 years old or younger were included in our study, and we cannot reach a significant conclusion about the gender-related difference in this age group.

It has been shown that the left hemisphere has a higher iron deposition than the right. It was thought that this asymmetry may reflect underlying hemispheric differences in iron requirements for dopamine metabolism and may be related to motor lateralization in humans^{19,23-26}. However, our results revealed significantly lower signal ratios and a higher chance of hypointensity in the right pulvinar region than on the left. Moreover, seven subjects had hypointensity only in the right pulvinar region, but no hypointensity was found only on the left. The reason is unknown. We speculate that the hemispheric difference in signal intensity that we detected may reflect and be related to some other physiological conditions in the brain apart from dopamine metabolism and motor lateralization. Haacke et al. demonstrated slightly more hypointense signal in the left pulvinar than the right. Although this was not as large an effect lateralizing to the left hemisphere as was seen with the putamen, caudate nucleus, globus pallidus and red nucleus²⁰. The reason for this difference is unknown and might be related to the R2 effect on our FLAIR images or differences in the patient populations evaluated.

Our results did show a positive linear association when signal ratios from the pulvinar region were compared with those in the putamen and globus pallidus, respectively. As in the putamen and globus pallidus, FLAIR signal decreases in the pulvinar region are likely significantly affected by iron. Our study also showed the same gender effect on the signal intensity in the pulvinar region, putamen, and globus pallidus. Male subjects had a more rapid decrease of signal ratio with age than females. As

to hemispheric asymmetry of signal changes, we did not find consistency among the pulvinar regions, putamina, and globus pallidi. More data are needed to confirm the asymmetry of signal changes in the pulvinar.

The central thalamus was used as a control structure in calculation of signal ratios because the thalamus shows no age-related iron increase based on previous studies^{18,19,22}. However, a recent study appears to potentially contradict this hypothesis since it found that iron in the whole thalamus increases linearly with age²⁰. The influence from the pulvinar on this measurement is not known because the whole thalamus including the pulvinar was evaluated and not the thalamus excluding the pulvinar²⁰. The authors did evaluate the pulvinar thalamus separately but it was not analyzed how this measurement affects the putative iron measurement of the whole thalamus²⁰. In addition, the thalamus adjacent to the pulvinar is visually used as a background for evaluating pulvinar hypointensity during clinical MR interpretation and this was the scenario we wanted our study to reflect. Our process does not contradict this routine method.

The purpose of this study was not to measure iron content but to evaluate the signal intensity change in the pulvinar on FLAIR at 3T given our clinical recognition of the phenomena and the diagnostic questions that this raised. Therefore we did not include any data from field-dependent and phase methods, which are more specific in measuring iron deposition in brain²⁷. Our work confirms a difference in the pulvinar region versus the whole thalamus in normal subjects. Clinicians need to be aware that these changes are easily visualized at 3T on FLAIR images and do not necessarily indicate the presence of pulvinar abnormality in MS, MSA-P and IPD⁴⁻⁸. When evaluating the thalamus or the posterior thalamus for R2 or R2* signal changes, researchers should be cognizant of this difference.

In conclusion, the physiological signal features of the pulvinar are complex and depend on age, gender, and hemispheric lateralization. We detected a significant association between the pulvinar signal on FLAIR imaging with age. There is a linear signal decrease with age. The positive linear association is found when signal change in the pulvinar region was compared with those in the putamen and globus pallidus, suggesting a similar pattern of signal changes. The study helps define the expected appearance of a normal pulvinar on FLAIR and this will be useful in the clinical setting.

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