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Original Article

Evaluation of physiologic pineal gland calcification via computed tomography in the pediatric population

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Abstract

Aim: To determine the area, density and morphology of physiologic pineal gland calcification in the preadolescents and adolescents using computed tomography and to evaluate correlations with age and sex.

Material and Methods: This retrospective study evaluated 220 cases (110 males, 110 females) with ages ranging from 7-17 years (mean age: 12±3.17). Cases were divided into two groups according to age of 7-12 years (n=120, preadolescent) and 13-17 years (n=100, adolescent). Morphology (homogeneous-heterogeneous), area (mm2) and density (Hounsfield Units [HU]) of pineal calcifications were investigated on computed tomography. Comparisons were made between age groups and sex in terms of these variables.

Results: This study found pineal calcification frequency was 50%, 35% and 67% in all cases, preadolescents, and adolescents, respectively. According to morphology, 60.9% of calcifications were homogeneous and 39.1% were heterogeneous. Median calcification area and density values were 8.50 (6-15) mm2 and 67 (50-109.75) HU, and 7 (4.75-14.25) mm2, and 67 (53.25-87.75) HU, for males and females, respectively, with no significant difference identified between the sexes (p=0.353 and p=0.463, respectively). Median calcification area in the preadolescent and adolescent age groups was 7 (6-12) and 10 (5-18) mm2, with no significant difference identified between the groups (p=0.175). Median density values were 70 (56-109) HU for adolescents and this was high compared to preadolescents (59 [47-78] HU) (p=0.005).

Conclusion: Physiologic pineal calcification frequency, area, density and morphology were revealed for preadolescent and adolescents. These values may be used as qualitative and quantitative reference data for differentiation of normal/abnormal pineal calcification in routine practice.

Keywords: Computed tomography; pediatric; physiologic calcification; pineal gland.

INTRODUCTION

Intracranial calcifications may by caused by mineral (for example, calcium) or metal (for example, iron) accumulations in blood, veins or cortex. Physiologic brain calcification is common. It may be observed at any age in any ethnic group and in males and females (1). Pathologic calcifications in the brain may occur with tuberculosis, toxoplasmosis, cysticercosis, primary intracranial tumors, metastatic lesions, autoimmune situations, infectious diseases, endocrine disorders like thyroid or parathyroid disease, and in neuropsychiatric situations related to seizures or strokes (2-4). Daghighi et al. (5) in a study of computed tomography (CT) of individuals aged from 15-85 years stated physiologic calcification rates were as follows; 71% pineal gland, 66.2% choroid plexus, 20.1% habenular, 7.3% tentorium cerebelli, sagittal sinus or falx cerebri, 6.6% vascular, 0.8% basal ganglion and 0.9% lens and other undefined structures. Among these calcifications, pineal calcification (PC) was the most commonly observed. The prevalence of PC in adults is reported to be in the interval 68.5-75.1% in many studies (6-8).

Roentgenograms were used for identification of intracranial calcifications and lesions containing calcium before CT. However, it is very difficult to identify small size calcifications with roentgenograms. With the development

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of noninvasive advanced imaging techniques like CT, it allowed the opportunity to evaluate many healthy and diseased anatomic structures and sizes in unrivalled manner (9-12). With the popularity of the use of CT, PC has begun to be encountered more frequently in routine practice. However, there are insufficient morphologic and numerical criteria for the differentiation of normal and abnormal PC in the pediatric period.

As a general guide, physiologic calcifications have millimetric size, smooth edges and are bilateral and symmetric around the midline, while pathologic calcifications have large size, irregular edges and are asymmetrical on CT (2,3). Among these findings, size has an important role (13). Just as physiologic PC may be purely homogeneous morphologically, in many cases it may be heterogeneous in fractured or fragmented form as a soft tissue component. These size estimations may cause misleading results. Some studies have used a computer-based mathematical algorithm to calculate estimated volume in multiple slices (14). Some of these measurements require computer software and may take time. As a result, we think measurement of the total area of PC dimensions on a single CT slice may be more practical and objective. To the best of our knowledge, there is no study in the literature investigating physiologic PC area on CT in pediatric cases.

The aim of this study was to investigate the area, density and morphology of physiologic PC on CT in the pediatric period and evaluate correlations with age and sex.

MATERIAL and METHODS

This study received permission from the local ethics committee (Decision no: 2018/270). The study was completed in accordance with the principles of the Helsinki Declaration. As the study was retrospective, "informed consent" was not received from parents. No personal information belonging to cases is given. Radiologic images are presented anonymously.

This single-center retrospective study investigated a total of 220 cases, 110 males and 110 females, with ages ranging from 7-17 years, with brain CT taken between March 2018 and March 2019. Computed tomography images were randomly selected from the hospital automation and archive system (PACS) and brain CT with any pathologic findings like brain mass, intracranial hemorrhage, edema, hydrocephalus, cranial malformation and atrophy were excluded. CT with pathologic calcification appearance like pineal gland asymmetry, very large size, and irregular edges were excluded. Children younger than 7 years were not included in the study. CTs with any movement or metal artefacts involving any region of the brain were excluded from the study. Cases with no known chronic disease, normal blood values (patient history such as blood values, consultation notes and surgery notes were reached through the hospital automation system), sufficient image quality and normal brain CT were included in the study. PC incidence was evaluated for all cases and in the age groups. Individuals with PC were investigated for calcification morphology (homogeneous-heterogeneous), area (mm2), and density (Hounsfield Units). In age groups, the quantitative normal data were determined for calcification area and density values. Additionally, the age groups were compared in terms of these variables.

CT protocol

Brain CT investigations were performed in supine position in a multislice CT scanner without contrast material (SOMATOM Definition Flash CT 256-slice scanner, Siemens Medical Solutions, Erlangen, Germany). Screening began from the foramen magnum. Images were taken in caudocranial direction. Imaging parameters were 100 kVp, 200 mA, slice thickness 5.0 mm, interval 20 mm, imaging area 23 (FOV), reconstruction interval 1.25 mm, and gantry rotation speed 1 s. Images had 90 HU window width and 45 HU window level using brain window settings with axial slices evaluated.

CT image analysis

Investigations were performed by a pediatric radiologist with more than 10 years pediatric brain CT experience. Firstly, PC_s were determined with visual assessment. Later, cases with calcification were divided into groups with homogeneous calcification and heterogeneous calcification. Homogeneous calcification had oval shape, pure rough calcific focus. These calcifications had free region of interest (ROI) drawn manually at the external margins on the slice with largest visual extent, and area and density values were measured (Figure 1). Heterogeneous calcifications comprised several punctate or amorphous shaped calcifications. From the external margin of these calcifications, ROI were drawn to include intercalcific hyperdense soft tissue areas with total area and HU values measured (Figure 2).

Statistical analysis

Analysis in the study was completed using SPSS Statistics 25.0 software (IBM Corp., NY, USA) and MedCalc 14.8.1 programs. The fit of quantitative variables to normal distribution was investigated with the Kolmogorov-Smirnov test. Independent groups were compared with the Mann Whitney U test. The presence of dependence between qualitative variables was investigated with the chi-square analysis. The presence of correlations between quantitative variables was determined with the Spearman correlation analysis. For prediction of calcification age values, the receiver operating characteristic (ROC) curve analysis was applied with the aim of determining the cut-off point and area under the curve. Descriptive statistics for qualitative variables are given as frequency (percentage), while mean ± standard deviation or median (25^{th}-75^{th} percentile) were used as descriptive statistics for quantitative variables. The level of statistical significance was determined as $p<0.05$.

RESULTS

Descriptive statistics for qualitative variables belonging to sex, age group, presence of calcification and calcification appearance are given in Table 1. Table 2 shows the descriptive statistics for quantitative variables of age, area and HU.

Table 1.Descriptive statistics of qualitative variables

VARIABLE		n (%)
Sex	Female	110 (50)
	Male	110 (50)
Age group	Preadolescent	120 (54.5)
	Adolescent	100 (45.5)
Presence of calcification	None	110 (50)
	Present	110 (50)
Calcification morphology	Homogeneous	67 (60.9)
	Heterogeneous	43 (39.1)

n (%) : frequency (percentage)

Median calcification area and density values were 8.50 (6-15) mm^2 and 67 (50-109.75) HU for girls and 7 (4.75-14.25) mm^2 and 67 (53.25-87.75) HU for boys. In terms of PC area and density values there was no statistically significant difference identified between girls and boys ($p>0.05$) (Table 3). Variation was not found between presence and morphology of calcification according to sex ($p>0.05$) (Table 3).

Table 2. Descriptive statistics of quantitative variables

Descriptive statistic	VARIABLE		
	Age (years) (n=220)	**Calcification area (mm2) (n=110)**	**HU (n=110)**
$\bar{X}$±SS	12±3.17	10.38±7.35	77.39±34.56

$\bar{X}$±SS: Mean ± standard deviation

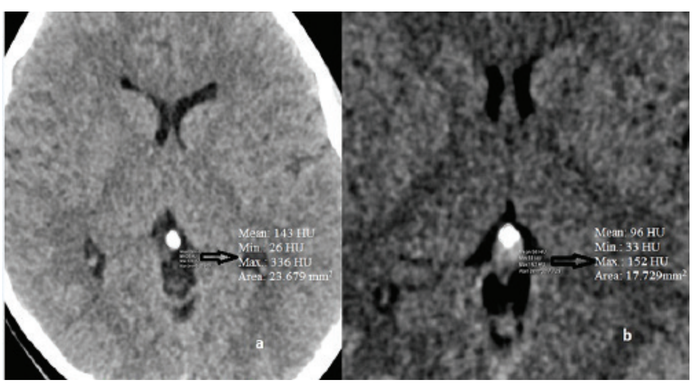

Figure 1. Homogeneous pineal calcification examples from 9-year old girl (a) and 11-year old boy. Boundaries of calcification are drawn, area and density measured.

Table 3. Descriptive statistics and comparison results for presence of calcification, appearance, area and mean HU values according to sex

		SEX		p
		Male	**Female**	
Calcification presence	Absent	52 (47.2)	58 (52.7)	0.345
	Present	58 (52.8)	52 (47.3)	
Calcification morphology	Homogeneous	33 (56.9)	34 (65.4)	0.475
	Heterogeneous	25 (43.1)	18 (34.6)	
Calcification area (mm2)		7 (4.75-14.25)	8.50 (6-15)	0.353
HU		67 (53.25-87.75)	67 (50-109.75)	0.463

Table 4. Descriptive statistics and comparison results for presence of calcification, and appearance according to age group

		AGE GROUP		p
		Preadolescent	**Adolescent**	
Calcification presence	Absent	77 (64.2)[a]	33 (33)[b]	**<0.001**
	Present	43 (35.8)[a]	67 (67)[b]	
Calcification morphology	Homogeneous	26 (60.5)	41 (61.2)	1.00
	Heterogeneous	17 (39.5)	26 (38.8)	

Different letters in the same row indicate differences between the groups

Findings for the presence and morphology of calcification in the preadolescent and adolescent age groups are given in Table 4. The presence of PC differed significantly according to age, and was more common in the adolescent period ($p<0.001$).

Correlation analysis results for age, calcification area and density values only found a statistically significant correlation between age and HU values. This correlation was positive but weak ($r=0.278$, $p=0.003$).

In terms of PC area in the preadolescent and adolescent age groups, no significant difference was determined ($p=0.175$). Density values were found to be significantly higher in the adolescent age group compared to the preadolescent group ($p=0.005$) (Figure 3).

The results of ROC analysis found the PC incidence frequency increased in individuals older than 11 years, with the area under the curve 70.3 br^2. The sensitivity for prediction of the presence of calcification using age was 70.91% and specificity was 61.82%. Age was determined to be a significant variable at advanced level for prediction of the presence of calcification ($p<0.001$) Figure 4).

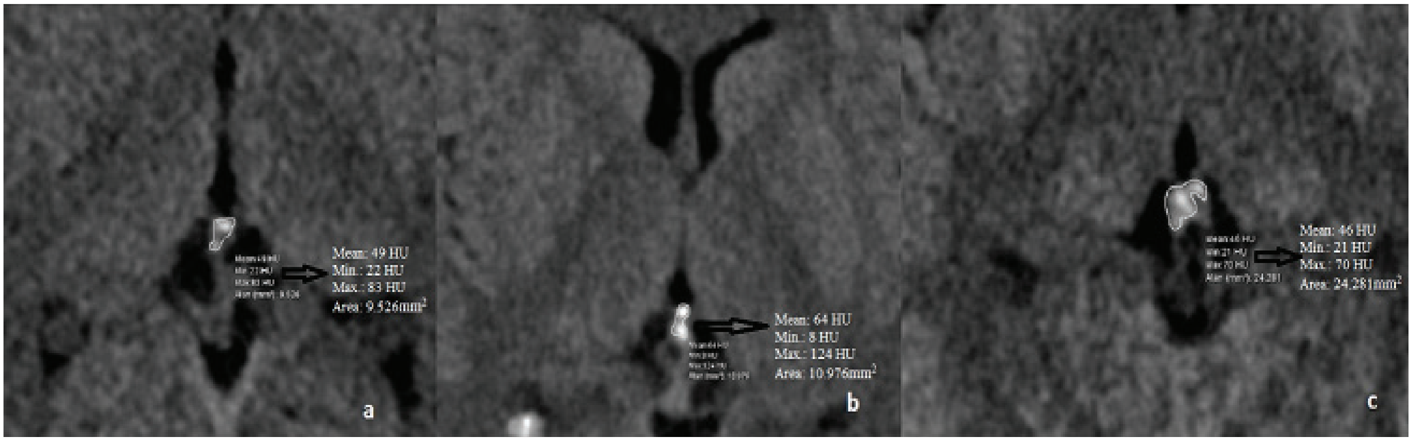

Figure 2. Heterogeneous pineal calcification examples from 12-year old boy (a), 13-year old boy (b) and 16-year old girl (c). External boundaries of punctate or amorphous clear calcification and total intercalcific hyperdense regions drawn, area and density measured

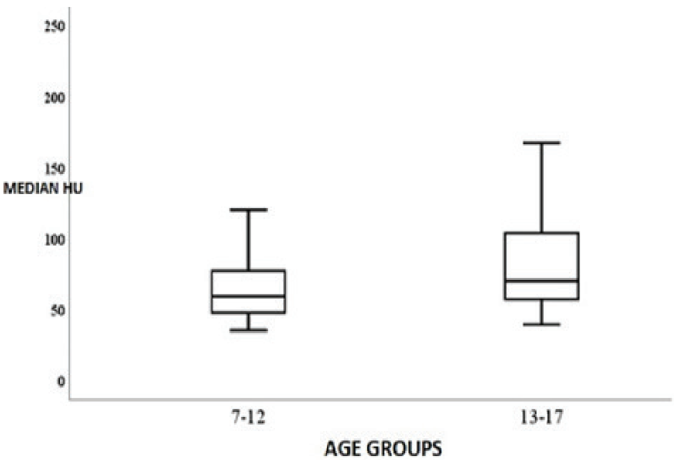

Figure 3. Box plot of density variation according to age group

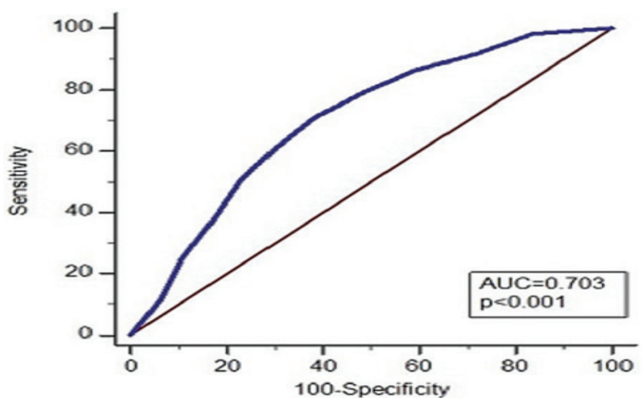

Figure 4. ROC graph of age values in prediction of calcification presence.

DISCUSSION

In this study, the incidence, morphology, area and density of physiologic PC in preadolescents and adolescents were evaluated with CT, and important results were determined. First, the general PC incidence is high in preadolescents and adolescents. Second, there were no significant differences identified between calcification area and density values between the sexes. Additionally, calcification presence and morphology did not differ between the sexes. Third, there were no differences found for calcification area between preadolescent and adolescent age groups. Fourth, density values were higher in adolescents than in preadolescents.

The pineal gland (pineal organ, epiphysis cerebri) is a small but important structure with the shape of a pine cone, accepted as a part of the epithalamus. Embryologically, it is derived by thickening of the ependyma in the posterior section of the third ventricle in the seventh week (15). It produces melatonin which affects wake/sleep patterns and modulation of seasonal functions. It is thought to be associated with reproductive functions and the onset of puberty. The pineal region is anatomically complicated, and may house many masses and tumors. Among these are cystic nonneoplastic lesions (pineal cysts, cavum veli interpositi, arachnoid cysts), parenchymal tumors (pineocytoma, pineoblastoma, papillary tumors of the pineal region), germ cell tumors (germinoma, embryonal carcinoma, choriocarcinoma, teratoma), metastasis, vascular lesions (Galen vein malformation, internal cerebral vein thrombosis) and other intracranial mass extensions (astrocytoma, meningioma) (16,17).

Before the use of CT, roentgenograms were beneficial for evaluation of intracranial calcifications. However, PC may be observed on less than half of conventional roentgenograms. The most sensitive radiologic method to identify pineal calcification is accepted as CT. With the increase in the use of CT in the pediatric period, this entity is encountered more often in routine practice (18). Since CT causes serious radiation exposure in the pediatric period, it would be advantageous to identify PC by magnetic resonance imaging (MRI). Apart from the absence of ionizing radiation, MRI provides superior soft tissue contrast and is a preferred method for evaluating the pineal region since it allows for the correct removal of pineal tumors before surgery. Recent advances in MRI imaging have led to the development of novel gradient echo (GRE) imaging techniques such as SWMR, which is based on magnetic susceptibility and sensitive to materials distorting the local magnetic field. SWMR allows for a reliable differentiation of calcifications from tissue artifacts, hemorrhage and other causes of susceptibility differences by using $T2^*$ weighted magnitude and GRE filtered-phase information to generate a unique contrast.

The pineal gland is located on the midline. Any change in location from the midline indicates the presence of a lesion taking up space in the intracranial cavity. The size of calcification is a warning sign for pathologic processes. Normal/abnormal pineal gland differentiation is frequently made visually. Good experience is required for accurate assessment. As a result, knowing the frequency and quantitative values for PC in some age groups will be beneficial and objective. This study will provide a significant contribution to the medical literature in terms of guidance for this purpose.

This study shows that the incidence of PC is high in the pediatric period and the incidence increases with age. Pathogenesis of pineal calcification includes calcified structures called the "brain cluster" or acevuli corpora arenacea within the pineal gland (19). Dominantly comprising calcium and magnesium salts, corpora arenacea are multiple in elderly patients. A study by Doyle & Anderson (20) found physiologic PC was present in 20% of the whole group, 39% of 8-14 year olds, 8% of those younger than 10 years and 1% in those younger than 6 years. A study investigating more than 700 healthy cases did not observe physiologic PC in those younger than 5 years with CT; however, they stated the prevalence increased logarithmically with age (21). In adolescence, the normal PC prevalence among 8-14-year olds is only from 8% to 11%, but reached 40% by 20 years of age. Similar to our study, the ages of individuals with calcification was mainly in the 13-17 year interval, with the ages of individuals without calcification observed mainly in the 7-12 year interval.

This study found high physiologic PC incidence (35.8%) among children under 10 years old. A study with roentgenogram by Chang et al. (22) proposed that PC was rare in children under the age of 10 years, but may be associated with tumors in the pineal gland like germinoma or teratoma. The reason for this contradiction may be explained by this study using roentgenogram and having lower technological sensitivity. On the basis of our results, with the condition of no pathologic size or findings on routine brain CT in preadolescent children, observations of pineal calcification should not be a surprise. This visual habit may ensure avoidance of invasive and unnecessary advanced tests.

According to this study, the presence and morphology of calcification in children was not found to be linked to sex. Similarly, Doyle & Anderson (20) in a study of a total of 242 cases younger than 16 years stated there was no difference in the pineal calcification rates between the sexes (male 34/159, female, 14/83). Differently, a study with mean age of 46.3 years including 11,941 dominantly adult cases stated PC was more common in males (1). Daghighi et al. (5) in a study from Iran with 1569 cases (age interval 15-85 years) identified the intracranial physiologic calcification frequency was higher in males compared to females. The reason for this is not clear. Some differences like lifestyle, hormonal, nutritional and social behavior between children and males may affect development of calcification.

This study found the density values in adolescents were higher by a significant degree compared to preadolescents. Similarly, a study of adults by Turgut et al. (8) visually separately defined calcified and noncalcified components of the pineal gland on axial CT slices. Then they measured density values with scoring. Findings showed the density of the calcified regions of the pineal gland increased with age. Beker-Acay et al. (14) measured total pineal volume, calcified pineal volume and noncalcified pineal volume in adults based on some age groups. The study found median value was 88.5 mm^3 (12.3 mm^3-411 mm^3) for total pineal volume, 74.3 mm^3 (12.3 mm^3-298 mm^3) for noncalcified pineal volume and 3.9 mm3 (0 mm^3-141 mm^3) for calcified pineal volume. Differently in our study, the size of the pineal gland was measured with area (mm^2) in children and normal total values were given for calcified and noncalcified regions. We think measurement of total area on a single CT slice will be more useful in routine practices and will save time. Additionally, the calcification area in our study was found not to differ significantly in the preadolescent and adolescent age groups. In terms of PC area and density values in females and males, there was no statistically significant differences identified. Knowing normal values will be a guide for both groups and sexes.

There are some limitations to our study. First is the low number of patients. Larger series may be used for studies of this topic. Secondly, the study did not include children younger than 7 years. Thirdly, the study was retrospective. Fourthly, clinical and laboratory data used to support the reality that the subjects were healthy were only obtained from the electronic archive system. Fifthly, measurements were made by a single radiologist and intermeasurement reliability was not evaluated.

CONCLUSION

In conclusion, the incidence and density of PC increase with age in children. The presence, area, density and morphology of pineal gland calcification are independent of sex. There were no significant differences in calcification area between preadolescent and adolescent age groups. Our study provides reference data for differentiation of pathologies progressing with possible calcification and physiologic calcification of the pineal gland in the pediatric period.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles according to the Declaration of Helsinki.

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REFERENCES

1. Yalcin A, Ceylan M, Bayraktutan OF, et al. Age and gender related prevalence of intracranial calcifications in CT imaging; datafrom 12,000 healthy subjects. J Chem Neuroanat 2016;78:20-4.
2. Vassilatou E, Pikounis V, Economopoulos T, et al. Extensive bilateral cerebral calcifications in a patient with primary hypoparathyroidism. Arch Neurol 2010;67:888-89.
3. Cañas CA, Tobón GJ. Multiple brain calcifications in a patient with systemic lupus erythematosus. Clin Rheumatol 2008;27:63-5.
4. Simoni M, Pantoni L, Pracucci G,et al. Prevalence of CT-detected cerebral abnormalities in an elderly Swedish population sample. Acta Neurol Scand 2008;118:260-67.
5. Daghighi MH, Rezaei V, Zarrintan S, et al. Intracranial physiological calcifications in adults on computed tomography in Tabriz, Iran. Folia Morphol (Warsz) 2007;66:115-19.
6. Admassie D, Mekonnen A. Incidence of normal pineal and chroids plexus calcification on brain CT (computerized tomography) at Tikur Anbessa Teaching Hospital Addis Ababa, Ethiopia. Ethiop Med J 2009;47:55-60.
7. Daghighi A, Tropp H. Computed tomography lung volume estimation and its relation to lung capacities and spine deformation. J Spine Surg 2019;5:132-41.
8. Turgut AT, Sönmez I, Cakıt BD, et al. Pineal gland calcification, lumbar intervertebral disc degeneration and abdominal aorta calcifying atherosclerosis correlate in low back pain subjects: A cross-sectional observational CT study. Pathophysiology 2008;15:31-9.
9. You S, Kim EY, Park KJ, et al. Visual assessment of calcification in solitary pulmonary nodules on chest radiography: correlation with volumetric quantification of calcification. Eur Radiol 2019;29:4324-32.
10. Gavrielides MA, Li Q, Zeng R,et al. Discrimination of Pulmonary Nodule Volume Change for Low- and High-contrast Tasks in a Phantom CT Study with Low-dose Protocols. Acad Radiol 2018;26:937-48.
11. Turgut AT, Karakaş HM, Ozsunar Y, et al. Age-related changes in the incidence of pineal gland calcification in Turkey: a prospective multicenter CT study. Pathophysiology 2008;15:41-8.
12. Taner L, Uzuner FD, Demirel O, et al. Volumetric and three-dimensional examination of sella turcica by cone-beam computed tomography: reference data for guidance to pathologic pituitary morphology. Folia Morphol (Warsz) 2019;78:517-23.
13. Sedghizadeh PP, Nguyen M, Enciso R. Intracranial physiological calcifications evaluated with cone beam CT. Dentomaxillofac Radiol 2012;41:675-78.
14. Beker-Acay M, Turamanlar O, Horata E, et al. Assessment of Pineal Gland Volume and Calcification in Healthy Subjects: Is it Related to Aging? J Belg Soc Radiol 2016;100:13.
15. Sumida M, Barkovich AJ, Newton TH. Development of the pineal gland: measurement with MR. AJNR Am J Neuroradiol 1996;17:233-36.
16. Westphal M, Emami P. Pineal lesions: a multidisciplinary challenge. Adv Tech Stand Neurosurg 2015;42:79-102.
17. Smith AB, Rushing EJ, Smirniotopoulos JG. From the archives of the AFIP: lesions of the pineal region: radiologic-pathologic correlation. Radiographics 2010;30:2001-20.
18. Bayrak S, Göller Bulut D, Kurşun Çakmak EŞ, et al. Cone Beam Computed Tomographic Evaluation of Intracranial Physiologic Calcifications. J Craniofac Surg 2019;30:510-13.
19. Vígh B, Szél A, Debreceni K, et al. Comparative histiology of pineal calcification. Histol Histopathol 1998;13:851-70.
20. Doyle AJ, Anderson GD. Physiologic calcification of the pineal gland in children on computed tomography: prevalence, observer reliability and association with choroid plexus calcification. Acad Radiol 2006;13:822-26.
21. Zimmerman RA, Bilaniuk LT. Age-related incidence of pineal calcification detected by computed tomography. Radiology 1982;142:659-62.
22. Chang CG, Kageyama N, Kobayashi T, et al. Pineal tumors: clinical diagnosis, with special emphasis on the significance of pineal calcification. Neurosurgery 1981;8:656-68.