Physiological Intracranial Calcifications in Children

A computed tomography-based study

Faiza Al Hajri,¹ Srinivasa Rao Sirasanagandla,² Ammar Boudaka,³ Humoud Al Dhuhli,⁴ *Eiman Al Ajmi⁴

¹Radiology Residency Program, Oman Medical Specialty Board, Muscat, Oman;
 Departments of ²Human & Clinical Anatomy, ³Physiology and ⁴Radiology & Molecular Imaging, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman.
*Corresponding Author’s e-mail: ealajmi@squ.edu.om

Abstract

Objectives: Physiological intracranial calcifications (PICs) are benign in nature and related to aging. We aimed to study the frequency of physiological intracranial calcifications (PICs) in pediatric population using computed tomography (CT). Methods: The brain CT scans of consecutive patients (age range, 0-15 years) who had visited Sultan Qaboos University Hospital from January 2017 to December 2020 were retrospectively assessed for the presence of PICs. The presence of calcifications was identified using 3 mm thick axial images, and coronal and sagittal reformats. Results: A total of 460 patients were examined and the mean age was 6.54 ± 4.94 years. The frequency of PIC in boys and girls was 35.1% and 35.4%, respectively. PICs were most common in choroid plexus with 35.21% (age range 0.4-15 years; median, 12 years), followed by the pineal gland in 21.08% (age range 0.5-15 years; median, 12 years) and the habenular nucleus in 13.04% of subjects (2.9-15 years; median, 12 years). PICs were less common in falx cerebri with 5.86% (age range 2.8-15 years; median, 13 years) and tentorium cerebelli in 3.04% (age range 7-15 years; median, 14 years) of subjects. PICs increased significantly with increasing age (p<0.001). Conclusion: Choroid plexus is the most frequent site of calcification. Choroid plexus and pineal gland calcifications may be present at less than 1 year of age. Recognizing PICs is clinically
important for radiologists as they can be mistaken for hemorrhage or pathological entities like neoplasms or metabolic diseases.

**Keywords**: Calcification; Pineal gland; Dura Mater; Brain; Computed Tomography

**Advances in Knowledge**
- This is the first study to evaluate physiological intracranial calcifications in Omani children.
- The choroid plexus is the most frequent site of physiological intracranial calcification.
- Choroid plexus and pineal gland calcifications may be present at less than 1 year of age.

**Application to Patient Care**
- The baseline data of PICs are clinically important for neuroradiologists and neurosurgeons as they can be mistaken for hemorrhage or pathological entities like neoplasms or metabolic diseases.

**Introduction**
Physiological intracranial calcifications (PICs) are benign in nature and typically occur with aging.¹ PICs are well known to occur in pineal gland, choroid plexus, habenula, dural folds: falx cerebri, and tentorium cerebelli, sagittal sinus, and petroclinoid ligaments.² Structurally, they are deposits of calcium and/or iron in the brain parenchyma or vasculature. PICs are not associated with any disease and/or underlying pathology.¹,² PICs are incidental findings in neuroimaging. PICs occurrence at all ages of life has been reported. PICs prevalence increases with age, and its prevalence varies between 50% and 70% in subjects older than 30 years.³ However, their prevalence is low in preadolescents³ and children⁴. They can be detected in both genders and any race or ethnic group.⁵ They can be detected by plain radiography, sonography, computed tomography (CT), and magnetic resonance imaging. However, CT is often preferred due to the hyperdense appearance of calcium deposits in this imaging.⁶,⁷

In general, PICs are smaller in size, and larger size (>1cm) calcifications should be suspected of having an underlying pathological cause.² Intracranial calcifications may be pathological due to a wide range of infectious, metabolic, neoplastic, and vascular etiologies or because of
prior brain insult. It has been reported that environmental factors such as altitude and sunlight exposure influence the pineal gland calcification (PGC) process. Till date, very few studies exist on the prevalence of PICs in the pediatric population, particularly choroid and dural calcifications. In children PICs are most commonly found in the choroid plexus and less commonly found in dural folds. Baseline data of PICs are clinically important for neuroradiologists and neurosurgeons as they can be mistaken for hemorrhage or pathological entities like neoplasms or metabolic diseases. Furthermore, the reported prevalence of PICs in children is varied among different studies. Despite having tremendous clinical significance, very few studies have been conducted on the prevalence of PICs in children. Hence, we aimed to study the frequency of PICs in Omani children using CT.

Materials and Methods

Study population
In this retrospective cross-sectional study, brain CT scans of consecutive Omani children aged ≤15 years who had visited Sultan Qaboos University Hospital (SQUH) during the period from January 2017 to December 2020 were assessed. Each patient's demographic information and diagnostic findings were obtained from the electronic medical records of SQUH. After applying inclusion and exclusion criteria, we included a total of 460 patients. Relevant patients’ clinical information was obtained. The most common clinical indications for CT examinations in our cohort were trauma, seizures, and headache. On the other hand, the exclusion criteria considered patients with known neuronal diseases, which were associated with calcifications, excessive motion artifacts, epithalamic masses, and cerebral hemorrhages. Patients with incomplete details and non-Omanis were also excluded from the study.

Acquisition protocol and data acquisition
All brain CT examinations were performed using 64-slice multidetector CT scanner (Siemens Sensation 64) with a slice collimation of 30 x 0.6 mm and a 512 x 512 matrix. The Picture Archiving and Communication System (PACS) (Synapse PACS, FUJIFILM Worldwide, version 5.7.102) was used for screening the images. The studies were reviewed by a single observer. In each case, presence of calcifications in the falx cerebri, tentorium cerebelli, epithalamus, and choroid plexus were analyzed using 3 mm thick axial images and coronal and sagittal reformats. Based on their distinct locations, epithalamic calcifications were identified separately as pineal or habenular calcifications. Falcine and tentorial calcifications
were identified along the dural folds. The side of choroid plexus calcification was noted whether unilateral or bilateral. Positive intracranial calcification in any of the areas mentioned above was defined by being of higher attenuation compared to the gray matter. The morphology of calcifications in the choroid plexus and the pineal gland was classified to single or punctate versus large or multiple. The Medical Research Ethics Committee, Sultan Qaboos University, Muscat approved the study and waived the requirement for written consent.

Statistical analysis
Statistical Package for the Social Sciences (SPSS, version 23.0, IBM Corporation, NY, USA) for Windows was used to present the data. The data was presented as mean and standard deviation. Chi-square test was used to determine the gender and age influence on frequency of PICs in different regions of the brain. The differences were considered significant at $p$ value <0.05.

Results
In the present study, PICs were examined in the CT scans of 460 children. The mean age of the subjects was 6.54 ± 4.94 years. The study subjects were categorised into five age groups: 0-3 years (179); 3.1-6 years (71); 6.1-9 years (69); 9.1-12 years (48); >12 years (93). PICs increased significantly with increasing age (p<0.001; [Figure 1]). Among the study subjects, 265 (57.6%) were boys, and 195 (42.4%) were girls. The frequency of PICs in boys and girls was 35.1% (93/265) and 35.4% (69/195), respectively. The gender influence on PICs frequency was not significant (p = 0.311). In Figure 2, the frequency of PICs in different regions of the brain (choroid plexus, pineal gland, habenular nucleus, falx cerebri, and tentorium cerebelli) in each year, is presented. Additionally, Table 1 depicts the age range of PIC occurrence in different regions of the brain. The highest frequency of PICs was observed in the choroid plexus with 35.21% (162/460). The age range of choroid plexus calcification was 0.4 -15 years (median, 12 years). Majority of choroid calcification morphology was either punctate or single, accounting for 90.7% (147/162) of the total, with large or multiple accounting for 9.3% (15/162). Choroid calcifications were found bilaterally in 84.57% (137/162) of subjects and in 11.1% (18/162) on the right side of cerebrum and 4.32% (7/162) on the left side. The overall epithalamic calcification frequency was 34.13% (157/460). Pineal gland calcification (PGC) was identified in 21.08% (97/460) of subjects with an age range of 0.5 to 15 years (median, 12 years). Majority of PGC morphology was punctate or
single with 83.51%, (81/97), followed by large or multiple with 16.49% (16/97). Habenular calcification was observed in 13.04% (60/470) of subjects with an age range of 2.9 - 15 years (median, 12 years). Dural calcifications were observed most frequently in the falx cerebri with 5.86% (27/460), followed by those in the tentorium cerebelli with 3.04% (14/460). The age range of falx cerebri and tentorium cerebelli calcifications was 2.8-15 years (median, 13 years) and 7-15 years (median, 14 years), respectively. Figure 3 and Figure 4 are the representative CT images showing PICs in different regions of the brain.

Discussion

Knowing the detectable age of PICs on imaging is crucial clinically, especially in the early years of life. The current study demonstrated that PICs are found in the pediatric population across all age groups with varying frequency.

The pineal gland is a part of the epithalamus located in the midline at the quadrigeminal cistern, close to the posterior end of the roof of the third ventricle. It secretes melatonin, serotonin, and N, N-dimethyl-tryptamine hormones and plays an important role in circadian rhythm regulation. Light stimuli regulate its secretory activity and are highly active during darkness. Histologically, PGC or corpora arenacea consist of by-products of pineal neuronal and glial polypeptide exocytosis, the exophytic membrane debris with surrounding calcification. These calcified concentrations are mainly composed of calcium and magnesium salts. PGC is known to appear early in life and increase gradually with advancing age. A histopathology study has documented the presence of PGC even in fetal life. Although the prevalence rate of PGC is high in adults, it is less prevalent in children. In a study by Helmke and Winkler, the reported frequency of PGC was 3% in the first year of life, and then it increased gradually to 7.1% in the first decade of life. In the same study, the frequency of PGC increased to 33% in 10-18 year age group. In a study by Doyle and Anderson, PGC was observed in 1% and 8% of subjects younger than 6 and 10 years old, respectively, and 39% in 8-14 years old subjects. In this study, the youngest patient with PGC was 3 years old. Similarly, in a study by Whitehead et al., the youngest patient with PGC was 3 years old. In this study PGC was observed only in 5% of children with an age range of 3.2 to 8.9 years. In a recent study by Caliskan and Ozturk, a high frequency of 35.8% PGC was observed in the 7-12 year age group, and it increased to 67% in the 13-17 year age group. In the present study, PGC was observed in 21.08% of subjects younger than 15 years.
Similar to previous studies, in our study, PGC frequency increased gradually with increasing age, with 7% in the 3-6 year age group and 51.6% in the 12-15 year age group, respectively. In our study, the youngest patient with PGC was 5 months old. PGC was observed only in four subjects younger than 3 years. To the best of our knowledge, this is the first time we observed PGC at a very young age using contemporary CT technology. In the previous study, in the majority of patients, PGC morphology was single or punctate (71%). Similarly, in our study, single or punctate PGC were the most common morphology pattern, with a frequency of 83.51%. The habenula is a bilaterally paired epithalamic nuclear complex situated close to the dorsomedial surface of the thalamus. It plays an important role in the limbic system and acts as a relay and processing center between the midbrain and the limbic system. Its calcifications generally appear as a curvilinear pattern with a prevalence rate of 15% in adults. The composition of these calcifications is found to be similar to that of the pineal gland with salts of calcium and magnesium. In a previous study, habenular calcifications were noted in 10% of subjects younger than 9 years old, and they were the most frequent site of calcification in the epithalamus. In contrast, we observed habenular calcifications only in 4.1% of the patients younger than 9 years of age. However, it increased to 8.9% in subjects aged 9-15 years. An association between habenular calcification and pathophysiology has been postulated as habenular calcifications are observed in schizophrenia patients. Hence, baseline data of habenular calcifications are clinically important.

The choroid plexus produces cerebrospinal fluid and helps in the removal of brain metabolic waste and xenobiotics. It is the major source of transferrin protein in the brain. The atria of the lateral ventricles are the most commonly affected sites of calcification, followed by the third or fourth ventricles. Similar to previous studies, in our study, choroid plexus calcification increased significantly with age. In a study by Kendall and Cavanagh, choroid plexus calcification was found in only 2% of subjects younger than 8 years. Modic et al. have noted choroid calcification in 0.5% of subjects younger than 10 years old. In a study by Doyle and Anderson, it was noted in 7% and 16% of subjects younger than 10 and 16 years, respectively. Whitehead et al. have noted the calcification in 12% of children younger than 9 years of age, and the youngest subject was less than 1 month old. In our study, choroid plexus calcification was the most common intracranial calcification, with a frequency of 35.21%. In subjects less than 9 years of age, it was noted in 35.1% of subjects. The youngest patient with choroid calcification was 4 months old. In the previous study by Whitehead et al., the majority of choroid plexus calcifications were single or punctate
Similarly, in our study, single or punctate choroid plexus calcifications were observed in majority of the subjects (83.51%). Furthermore, choroid calcifications were found bilaterally in majority of the subjects. Various pathological conditions such as intraventricular infection, inflammation, hemorrhage, chronic calcium and phosphate imbalance are known to be associated with premature choroid plexus mineralization. Hence, age thresholds of normally expected choroid plexus calcification are clinically important to distinguish physiology from pathology. 

In children, PICs in falx cerebri and tentorium cerebelli are rare, and is often identified as an incidental finding during routine brain CT examination. In the skull radiographs of adults, calcification of falx cerebri was observed in 7% of subjects. In two different CT studies of adults, dural calcifications were observed in 7.3% and 12.5% of subjects, with a male dominance. To the best of our knowledge, physiological calcifications in the dural folds in children have been reported only in two studies. In a study by Kendall and Cavanagh, dural calcifications were observed in 0.8% of subjects less than 15 years of age. In another study by Whitehead et al., it was observed in 1% of subjects less than 9 years of age. In this study, dural calcifications were most prevalent in tentorium cerebelli followed by falx cerebri. 

In contrast, we observed 5.86% in falx cerebri and 3.04% in tentorium cerebelli. Furthermore, falx cerebri and tentorium cerebelli calcifications are not present in less than 2 and 7 years, respectively. As falx cerebri is formed from pluripotent embryonic mesenchymal stem cells, any external stimuli including, irritation, trauma, and haemorrhage would predispose these mesenchymal cells to transform into osteogenic cells, resulting in falcine ossification. The extensive dural calcifications are known to be associated with a few pathological conditions, particularly basal cell nevus syndrome. There is inconsistency in the existing literature regarding gender influence on the occurrence of PICs in the paediatric population. In a study by Whitehead et al., no significant gender difference (p=0.41) was observed. Two other studies by Doyle & Anderson and Caliskan and Ozturk, found no evidence of a gender effect on PGC calcification. Similarly, in the present study, gender influence on intracranial calcification was not observed. In contrast, two studies have reported a significant gender influence with male dominance. Further research needs to be conducted to draw a conclusive result in this regard. The prior knowledge of reference values of PICs in children is clinically important as this may frequently interfere with the differential diagnosis of metabolic mineralization, intracranial hemorrhage, and tumours. The following are some of
the limitations of this study. The volume, or CT density of PIC could not be performed. The study sample may not be representative of the Omani population because it is a single-centered study. A multi-centered study involving subjects from various parts of Oman and analysis of calcification quantification would be interesting.

Conclusion
The study provides the reference values for PICs in the Omani paediatric population. PICs are detected in all age groups of the paediatric population. The choroid plexus is the most frequent site of calcification, and it is bilateral. Choroid plexus and pineal gland calcifications may be present at less than one year of age. Calcifications in dural folds are relatively less common and are not present at less than 2 years of age. The baseline data of PICs are clinically important for neuroradiologists as they can be mistaken for hemorrhage or pathological entities like neoplasms or metabolic diseases.

Conflicts of interest
The authors declare that they have no conflict of interest

Funding
No funding was received for this study.

Author Contributions
Conceptualization and methodology was done by SRS and EA. Validation was done by EA and HA. Formal analysis was performed by SRS and AB and investigation was done by FA. FA and EA curated the data. The original manuscript draft preparation was done by SRS and the revision and editing were done by EA, HA and AB. Visualization was done by FA, SRS and EA and supervised by EA. The project administration was handled by EA, SRS and HA. All authors approved the final version of the manuscript.

Acknowledgment
We would like to thank Dr Sadhana Roychoudhury for her assistance in English editing. The present study has been presented at the 20th Congress of the International Federation of Associations of Anatomists, held in Istanbul, Turkey.

References


Figure 1. The frequency of physiological intracranial calcification in different age groups. The total number of patients analyzed was 460. Note calcification increased with increasing age (Chi square test; p<0.1).
Figure 2: The frequency of physiological intracranial calcifications among the 460 patients across different ages.
Figure 3. Examples of intracranial calcifications from the study. Axial CT images of the brain show (A) focal calcification in the falx (arrow), (B) bilateral calcifications of the choroid plexus in the trigones of the lateral ventricles (arrows), (C) habenular calcification (small arrow), and large pineal calcification (large arrow). (D) Reformatted coronal CT image of the brain shows right tentorial calcification (arrow).

Figure 4: Punctate calcifications versus large calcifications in the choroid plexus. (A) Axial CT image of the brain shows punctate calcifications in the choroid plexuses (arrows). (B) CT image in another patient demonstrates large choroid plexus calcifications (arrows).
Table 1. The age ranges of physiological intracranial calcifications at different regions of brain.

<table>
<thead>
<tr>
<th>Location of Calcification</th>
<th>No. of Patients</th>
<th>Age Range (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falx cerebri</td>
<td>27/460</td>
<td>2.8-15 (median, 13)</td>
</tr>
<tr>
<td>Tentorium</td>
<td>14/460</td>
<td>7-15 (median, 14)</td>
</tr>
<tr>
<td>Choroid Plexus</td>
<td>162/460</td>
<td>0.4 -15 (median, 12)</td>
</tr>
<tr>
<td>Pineal Gland</td>
<td>97/460</td>
<td>0.5 -15 (median, 12)</td>
</tr>
<tr>
<td>Habenula</td>
<td>60/460</td>
<td>2.9 -15 (median, 12)</td>
</tr>
</tbody>
</table>