CLINICAL & BASIC RESEARCH

Physiological Intracranial Calcifications in Children A computed tomography-based study

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ABSTRACT: *Objectives:* This study aimed to examined the frequency of physiological intracranial calcifications (PICs) in paediatric 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, Muscat, Oman, 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, with a mean age of 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, observed in 35.2% (age range: 0.4-15 years, median: 12 years) of subjects, followed by the pineal gland in 21.1% (age range: 0.5-15 years, median: 12 years) and the habenular nucleus in 13.0% of subjects (age range: 2.9-15 years; median: 12 years). PICs were less common in falx cerebri, observed in 5.9% (age range: 2.8-15 years; median: 13 years) of subjects, and tentorium cerebelli, observed in 3.0% (age range: 7-15 years, median: 14 years) of subjects. PICs increased significantly with increase in age (P < 0.001). *Conclusion:* Choroid plexus is the most frequent site of calcification. Choroid plexus and pineal gland calcifications may be present in infants younger than one year. Recognising PICs is clinically important for radiologists as they can be mistaken for haemorrhage or pathological entities such as neoplasms or metabolic diseases.

Keywords: Calcification; Pineal Gland; Dura Mater; Brain; Computed Tomography, Oman.

Advances in Knowledge

- The choroid plexus is the most frequent site of physiological intracranial calcifications (PIC) in Omani children.
- Choroid plexus and pineal gland calcifications may be present in infants younger than one year.
- **Application to Patient Care**

The baseline data on PICs are clinically important for neuroradiologists and neurosurgeons as they can be mistaken for haemorrhage or pathological entities such as neoplasms or metabolic diseases.

HYSIOLOGICAL INTRACRANIAL CALCIFICATIONS (PICs) are benign in nature and typically occur with aging.1 It is well known that PICs occur in pineal gland, choroid plexus, habenula and dural folds, including falx cerebri, 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 and have been reported to occur in all age groups. Their prevalence increases with age, varying between 50% and 70% in subjects older than 30 years.1 However, their prevalence is low in preadolescents and children.3,4 They can be detected in both genders and in any race or ethnic group.⁵ PICs 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, so larger calcifications (>1 cm) 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 aetiologies or because of prior brain insult.8 It has been reported that environmental factors such as altitude and sunlight exposure influence the pineal gland calcification (PGC) process.9 Till date, very few studies exist on the prevalence of PICs, particularly choroid and dural calcifications, in the paediatric population.4,10 In children PICs are most commonly found in the choroid plexus and less commonly in the dural folds.⁴ Baseline data on PICs are clinically important for neuroradiologists and neurosurgeons as they can be mistaken for haemorrhage or pathological entities such as neoplasms or metabolic diseases. Furthermore, the prevalence of PICs in children as reported by different studies varies considerably. Despite having tremendous clinical significance, very

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few studies have been conducted on the prevalence of PICs in children. Hence, the present study aimed to investigate the frequency of PICs in Omani children using CT.

Methods

This retrospective cross-sectional study assessed brain CT scans of consecutive Omani children aged ≤15 years who had visited Sultan Qaboos University Hospital (SQUH), Muscat, Oman, during the period from January 2017 to December 2020. Each patient's demographic information and diagnostic findings were obtained from the electronic medical records of SQUH. The most common clinical indications for CT examinations in the 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 artefacts, epithalamic masses and cerebral haemorrhages. Non-Omanis and patients with incomplete details were also excluded from the study.

All brain CT examinations were performed using 64-slice multidetector CT scanner, Siemens Sensation 64 (Siemens, Munich, Germany) with a slice collimation of 30 \times 0.6 mm and a 512 \times 512 matrix. The Picture Archiving and Communication System (PACS), Version 5.7.102 (Synapse PACS, FUJIFILM Worldwide, Tokyo, Japan) 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 analysed 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. It was noted whether the choroid plexus calcifications were unilateral or bilateral. Positive intracranial calcification in any of the areas mentioned above was defined as being of higher attenuation compared to the grey matter.⁴ The morphology of calcifications in the choroid plexus and the pineal gland was classified into single or punctate and large or multiple.4

The Statistical Package for the Social Sciences (SPSS), Version 23.0 (IBM Corporation, Armonk, New York, USA) was used to present the data. The data were presented as mean and standard deviation. A Chi-squared test was used to determine the influence of gender and age on the frequency of PICs in different regions of the brain. The differences were considered significant at a *P* value <0.05.

The Medical Research Ethics Committee, Sultan Qaboos University, Muscat, Oman, approved the study and waived the requirement for written consent (SQU-EC/498/2021).

Results

The PICs in the CT scans of 460 children were included and their clinical information was obtained. The mean age of the subjects was 6.54 ± 4.94 years. The study subjects were categorised into five age groups: 0-3 years (n = 179), 3.1-6 years (n = 71), 6.1-9 years (n = 69), 9.1–12 years (n = 48) and >12 years (n = 93). PICs increased significantly with increase in 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% (n = 93/265) and 35.4%(n = 69/195), respectively. However, the influence of gender on the frequency of PICs was not significant (P = 0.311) [Figure 2]. Additionally, Table 1 depicts the age range for the occurrence of PIC in different regions of the brain. The highest frequency of PICs was observed in the choroid plexus at 35.2% (n= 162/460). The age range of choroid plexus calcification was 0.4-15 years (median: 12 years). The majority of choroid calcification morphology was either punctate or single, accounting for 90.7% (n = 147/162) of the total, with large or multiple accounting for 9.3% (n= 15/162). Choroid calcifications were found bilaterally in 84.6% (n = 137/162) of subjects, on the right side of the cerebrum in 11.1% (n = 18/162) and on the left side in 4.3% (n = 7/162). The overall epithalamic calcification frequency was 34.1% (n = 157/460). PGC was identified in 21.1% (n = 97/460) of subjects, with an age range of 0.5-15 years (median: 12 years). The majority of PGC morphology was punctate or single, with a frequency of 83.5% (n = 81/97), followed by large or multiple accounting for 16.5% (n = 16/97). Habenular calcification was observed in 13.0% (n = 60/470) of subjects, with an age range of 2.9-15 years

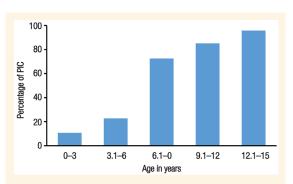


Figure 1: The frequency of physiological intracranial calcification in different age groups. Note that calcification increased with increase in age (Chi-squared test; P <0.01). *PIC* = *physiological intracranial calcification*.

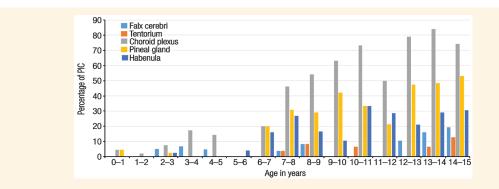


Figure 2: The frequency of physiological intracranial calcifications among the 460 patients across different ages. *PIC = physiological intracranial calcification.*

(median: 12 years). Dural calcifications were observed most frequently in the falx cerebri, with a frequency of 5.9% (n = 27/460), followed by the tentorium cerebelli, with a frequency of 3.0% (n = 14/460). The age range of falx cerebri and tentorium cerebelli calcifications

 Table 1: The age ranges of physiological intracranial calcifications at different regions of the brain

Location of calcification	n (%)*	Age range in years (median)
Falx cerebri	27 (5.8)	2.8-15 (13)
Tentorium	14 (3.0)	7-15 (14)
Choroid Plexus	162 (35.2)	0.4–15 (12)
Pineal Gland	97 (21.1)	0.5–15 (12)
Habenula	60 (13.0)	2.9–15 (12)

*Percentage does not add up to 100 as some patients had no calcifications while others had more than one type of calcification.

was 2.8–15 years (median: 13 years) and 7–15 years (median: 14 years), respectively [Figures 3 and 4].

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 paediatric 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.^{11,12} Light stimuli regulate its secretory activity and are highly active during darkness.^{11,12} Histologically,

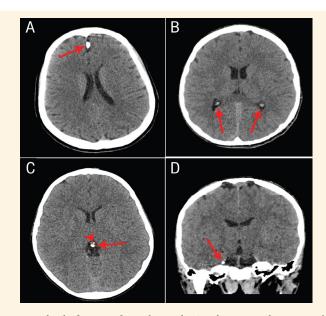


Figure 3: Examples of intracranial calcifications from the study. Axial computed tomography (CT) images of the brain showing (**A**) focal calcification in the falx (arrow), (**B**) bilateral calcifications of the choroid plexus in the trigones of the lateral ventricles (arrows), (**C**) habenular calcification (arrowhead) and large pineal calcification (arrow). Reformatted coronal CT image of the brain showing (**D**) right tentorial calcification (arrow).

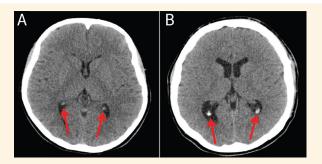


Figure 4: Punctate calcifications versus large calcifications in the choroid plexus. Axial computed tomography (CT) image of the brain showing (A) punctate calcifications in the choroid plexuses (arrows) and (B) CT image in another patient demonstrating large choroid plexus calcifications (arrows).

PGC or corpora arenacea consists of by-products of pineal neuronal and glial polypeptide exocytosis, the exophytic membrane debris with surrounding calcification.13 These calcified concentrations are mainly composed of calcium and magnesium salts.14 PGC is known to appear early in life and increase gradually with advancing age. A histopathological study has documented the presence of PGC even in fetal life.¹⁵ Although the prevalence rate of PGC is high in adults, it is less prevalent in children.9 In a study by Winkler and Helmke, frequency of PGC was reported to be 3% in the first year of life and then it was found to increase gradually to 7.1% in the first decade of life.¹⁶ The same study also found that the frequency of PGC increased to 33% in the 10-18 years age group.¹⁶ 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 in 39% of subjects in the age group of 8–14 years. In that study, the youngest patient with PGC was three years old.¹⁰ Similarly, the youngest patient with PGC was three years old in a study by Whitehead et al.4 In that study, PGC was observed only in 5% of children in the age range of 3.2-8.9 years. In a recent study by Caliskan and Ozturk, the frequency of PGC in the 7-12 years age group was observed to be high at 35.8% and it increased to 67% in the 13-17 years age group.³ In the present study, PGC was observed in 21.1% of subjects younger than 15 years of age.

Similar to previous studies, in the present study, PGC frequency increased gradually with an increase in age, with 7% in the 3–6 years age group and 51.6% in the 12–15 years age group, respectively. In this study, the youngest patient with PGC was five months old. PGC was observed only in four subjects younger than three years of age. To the best of the authors' knowledge, this is the first time PGC was observed at a very young age using contemporary CT technology. In a previous study, PGC morphology in the majority of patients was single or punctate (71%).⁴ Similarly, in the present study, single or punctate PGC

was 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 centre between the midbrain and the limbic system.¹⁷ Its calcifications generally appear as a curvilinear pattern, with a prevalence rate of 15% in adults.1 The composition of these calcifications is found to be similar to that of the pineal gland, with salts of calcium and magnesium.14 In a previous study, habenular calcifications were noted in 10% of subjects younger than nine years old and it was the most frequent site of calcification in the epithalamus.⁴ In contrast, the present study observed habenular calcifications only in 4.1% of patients younger than nine 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.¹⁸⁻²⁰ Hence, baseline data on habenular calcifications are clinically important.

The choroid plexus produces cerebrospinal fluid and helps in the removal of brain metabolic waste and xenobiotics.²¹ It is the major source of transferrin protein in the brain.²² The atria of the lateral ventricles are the most commonly affected sites of calcification, followed by the third or fourth ventricles.¹ Similar to previous studies, in the present study, choroid plexus calcification was found to increase significantly with age.^{23,24} In a study by Kendall and Cavanagh, choroid plexus calcification was found in only 2% of subjects younger than eight years of age.²⁴ Modic et al. noted choroid calcification in 0.5% of subjects younger than 10 years old, while a study by Doyle and Anderson observed its presence in 7% and 16% of subjects younger than 10 and 16 years of age, respectively.^{10,25} Whitehead et al. noted the calcification in 12% of children younger than nine years of age, with the youngest subject being less than one month old.⁴ In the present study, choroid plexus calcification was

the most common intracranial calcification, with a frequency of 35.21%. It was noted in 35.1% of subjects aged less than nine years. The youngest patient with choroid calcification was four months old. In a previous study by Whitehead et al., the majority (93.1%) of choroid plexus calcifications were single or punctate.⁴ Similarly, in the present study, single or punctate choroid plexus calcifications were observed in the majority of subjects (83.5%). Furthermore, choroid calcifications were found bilaterally in the majority of subjects. Various pathological conditions such as intraventricular infection, inflammation, haemorrhage, chronic calcium and phosphate imbalance are known to be associated with premature choroid plexus mineralisation. Hence, age thresholds of normally expected choroid plexus calcification are clinically important to distinguish physiology from pathology.4

In children, PICs in falx cerebri and tentorium cerebelli are rare and are often identified as an incidental finding during routine brain CT examinations.²⁶ In the skull radiographs of adults, calcification of falx cerebri was observed in 7% of subjects.^{27,28} In two different CT studies of adults, dural calcifications were observed in 7.3% and 12.5% of subjects, respectively, with a male dominance.^{5,29} To the best of the authors' 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 old.24 In another study by Whitehead et al., it was observed in 1% of subjects less than nine years old, with the most prevalence being observed in tentorium cerebelli, followed by falx cerebri.4

In contrast, the present study observed dural calcifications in the falx cerebri of 5.8% of subjects, while in 3.0% of subjects it was observed in tentorium cerebelli. Furthermore, falx cerebri and tentorium cerebelli calcifications were not present in subjects less than two and seven years old, 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.^{30,31} The extensive dural calcifications are known to be associated with a few pathological conditions, particularly basal cell nevus syndrome.32 There is inconsistency in the existing literature regarding the influence of gender on the occurrence of PICs in the paediatric population. In a study by Whitehead et al., no significant difference (P = 0.41) was observed between the genders.⁴ Two other previous studies found no evidence of the effect of gender on PGC calcification.3,10 Similarly, in the present study, the influence of gender on intracranial calcification was not observed. In contrast, two other studies have reported a significant influence of gender, suggesting a male dominance.^{5,29} 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 mineralisation, intracranial haemorrhage and tumours.

One of the limitations of this study is that the volume or CT density of PIC could not be measured. Furthermore, being a single-centre study, the study sample may not be representative of the Omani population. A multi-centre study involving subjects from various parts of Oman with an analysis of calcification quantification could reveal more informative results.

Conclusion

This study presented reference values for PICs in the Omani paediatric population. PICs were detected in all age groups of the paediatric population. The choroid plexus was found to be the most frequent site of calcification, where it was observed bilaterally. Choroid plexus calcifications and PGCs may be present in infants younger than one year. Calcifications in dural folds were found to be relatively less common and they were not present in individuals less than two years of age. The baseline data on PICs are clinically important for neuroradiologists as they can be mistaken for haemorrhage or pathological entities such as neoplasms or metabolic diseases.

AUTHORS' CONTRIBUTION

SRS and EA conceptualised the study and formulated the methodology. EA and HA validated the study. SRS and AB performed the formal analysis and FA conducted the investigation. FA and EA curated the data. SRS prepared the original manuscript draft, which was revised and edited by EA, HA and AB. Visualisation was performed 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.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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