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6 7 **Physiological Intracranial Calcifications in Children**

8 *A computed tomography-based study*

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17 18 **Abstract**

19 **Objectives:** Physiological intracranial calcifications (PICs) are benign in nature and related to
20 aging. We aimed to study the frequency of physiological intracranial calcifications (PICs) in
21 pediatric population using computed tomography (CT). **Methods:** The brain CT scans of
22 consecutive patients (age range, 0-15 years) who had visited Sultan Qaboos University
23 Hospital from January 2017 to December 2020 were retrospectively assessed for the presence
24 of PICs. The presence of calcifications was identified using 3 mm thick axial images, and
25 coronal and sagittal reformats. **Results:** A total of 460 patients were examined and the mean
26 age was 6.54 ± 4.94 years. The frequency of PIC in boys and girls was 35.1% and 35.4%,
27 respectively. PICs were most common in choroid plexus with 35.21% (age range 0.4 -15
28 years; median, 12 years), followed by the pineal gland in 21.08% (age range 0.5 -15 years;
29 median, 12 years) and the habenular nucleus in 13.04% of subjects (2.9 -15 years; median, 12
30 years). PICs were less common in falx cerebri with 5.86% (age range 2.8-15 years; median,
31 13 years) and tentorium cerebelli in 3.04% (age range 7-15 years; median, 14 years) of
32 subjects. PICs increased significantly with increasing age ($p < 0.001$). **Conclusion:** Choroid
33 plexus is the most frequent site of calcification. Choroid plexus and pineal gland

34 calcifications may be present at less than 1 year of age. Recognizing PICs is clinically
35 important for radiologists as they can be mistaken for hemorrhage or pathological entities like
36 neoplasms or metabolic diseases.

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

38

39 **Advances in Knowledge**

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

45

46 **Application to Patient Care**

- 47 • The baseline data of PICs are clinically important for neuroradiologists and
48 neurosurgeons as they can be mistaken for hemorrhage or pathological entities
49 like neoplasms or metabolic diseases.

50

51 **Introduction**

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

64

65 In general, PICs are smaller in size, and larger size (>1cm) calcifications should be suspected
66 of having an underlying pathological cause.² Intracranial calcifications may be pathological

67 due to a wide range of infectious, metabolic, neoplastic, and vascular etiologies or because of
68 prior brain insult.⁸ It has been reported that environmental factors such as altitude and
69 sunlight exposure influence the pineal gland calcification (PGC) process.⁹ Till date, very few
70 studies exist on the prevalence of PICs in the pediatric population, particularly choroid and
71 dural calcifications.^{4,10} In children PICs are most commonly found in the choroid plexus and
72 less commonly found in dural folds.⁴ Baseline data of PICs are clinically important for
73 neuroradiologists and neurosurgeons as they can be mistaken for hemorrhage or pathological
74 entities like neoplasms or metabolic diseases. Furthermore, the reported prevalence of PICs in
75 children is varied among different studies. Despite having tremendous clinical significance,
76 very few studies have been conducted on the prevalence of PICs in children. Hence, we
77 aimed to study the frequency of PICs in Omani children using CT.

78

79 **Materials and Methods**

80 *Study population*

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

92

93 *Acquisition protocol and data acquisition*

94 All brain CT examinations were performed using 64-slice multidetector CT scanner (Siemens
95 Sensation 64) with a slice collimation of 30 x 0.6 mm and a 512 x 512 matrix. The Picture
96 Archiving and Communication System (PACS) (Synapse PACS, FUJIFILM Worldwide,
97 version 5.7.102) was used for screening the images. The studies were reviewed by a single
98 observer. In each case, presence of calcifications in the falx cerebri, tentorium cerebelli,
99 epithalamus, and choroid plexus were analyzed using 3 mm thick axial images and coronal
100 and sagittal reformats. Based on their distinct locations, epithalamic calcifications were

101 identified separately as pineal or habenular calcifications. Falcine and tentorial calcifications
102 were identified along the dural folds. The side of choroid plexus calcification was noted
103 whether unilateral or bilateral. Positive intracranial calcification in any of the areas
104 mentioned above was defined by being of higher attenuation compared to the gray matter.⁴
105 The morphology of calcifications in the choroid plexus and the pineal gland was classified to
106 single or punctate versus large or multiple.⁴ The Medical Research Ethics Committee, Sultan
107 Qaboos University, Muscat approved the study and waived the requirement for written
108 consent.

110 **Statistical analysis**

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

117 **Results**

118 In the present study, PICs were examined in the CT scans of 460 children. The mean age of
119 the subjects was 6.54 ± 4.94 years. The study subjects were categorised into five age groups:
120 0-3 years (179); 3.1-6 years (71); 6.1-9 years (69); 9.1-12 years (48); >12 years (93). PICs
121 increased significantly with increasing age ($p < 0.001$; [Figure 1]). Among the study subjects,
122 265 (57.6%) were boys, and 195 (42.4%) were girls. The frequency of PICs in boys and girls
123 was 35.1% (93/265) and 35.4% (69/195), respectively. The gender influence on PICs
124 frequency was not significant ($p = 0.311$). In Figure 2, the frequency of PICs in different
125 regions of the brain (choroid plexus, pineal gland, habenular nucleus, falx cerebri, and
126 tentorium cerebelli) in each year, is presented. Additionally, Table 1 depicts the age range of
127 PIC occurrence in different regions of the brain. The highest frequency of PICs was observed
128 in the choroid plexus with 35.21% (162/460). The age range of choroid plexus calcification
129 was 0.4 -15 years (median, 12 years). Majority of choroid calcification morphology was
130 either punctate or single, accounting for 90.7% (147/162) of the total, with large or multiple
131 accounting for 9.3% (15/162). Choroid calcifications were found bilaterally in 84.57%
132 (137/162) of subjects and in 11.1% (18/162) on the right side of cerebrum and 4.32% (7/162)
133 on the left side. The overall epithalamic calcification frequency was 34.13% (157/460).
134 Pineal gland calcification (PGC) was identified in 21.08% (97/460) of subjects with an age

135 range of 0.5 to 15 years (median, 12 years). Majority of PGC morphology was punctate or
136 single with 83.51%, (81/97), followed by large or multiple with 16.49% (16/97). Habenular
137 calcification was observed in 13.04% (60/470) of subjects with an age range of 2.9 -15 years
138 (median, 12 years). Dural calcifications were observed most frequently in the falx cerebri
139 with 5.86% (27/460), followed by those in the tentorium cerebelli with 3.04% (14/460). The
140 age range of falx cerebri and tentorium cerebelli calcifications was 2.8-15 years (median, 13
141 years) and 7-15 years (median, 14 years), respectively. Figure 3 and Figure 4 are the
142 representative CT images showing PICs in different regions of the brain.

143

144 **Discussion**

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

148

149 The pineal gland is a part of the epithalamus located in the midline at the quadrigeminal
150 cistern, close to the posterior end of the roof of the third ventricle. It secretes melatonin,
151 serotonin, and N, N-dimethyl-tryptamine hormones and plays an important role in circadian
152 rhythm regulation.^{11,12} Light stimuli regulate its secretory activity and are highly active during
153 darkness.^{11,12} Histologically, PGC or corpora arenacea consist of by-products of pineal
154 neuronal and glial polypeptide exocytosis, the exophytic membrane debris with surrounding
155 calcification.¹³ These calcified concentrations are mainly composed of calcium and
156 magnesium salts.¹⁴ PGC is known to appear early in life and increase gradually with
157 advancing age. A histopathology study has documented the presence of PGC even in fetal
158 life.¹⁵ Although the prevalence rate of PGC is high in adults, it is less prevalent in children.⁹
159 In a study by Helmke and Winkler, the reported frequency of PGC was 3% in the first year of
160 life, and then it increased gradually to 7.1% in the first decade of life.¹⁶ In the same study, the
161 frequency of PGC increased to 33% in 10-18 year age group.¹⁶ In a study by Doyle and
162 Anderson, PGC was observed in 1% and 8% of subjects younger than 6 and 10 years old,
163 respectively, and 39% in 8-14 years old subjects.¹⁰ In this study, the youngest patient with
164 PGC was 3 years.¹⁰ Similarly, in a study by Whitehead et al., the youngest patient with PGC
165 was 3 years old.⁴ In this study PGC was observed only in 5% of children with an age range of
166 3.2 to 8.9 years.⁴ In a recent study by Caliskan and Ozturk, a high frequency of 35.8% PGC
167 was observed in the 7-12 year age group, and it increased to 67% in the 13-17 year age
168 group.³ In the present study, PGC was observed in 21.08% of subjects younger than 15 years.

169

170 Similar to previous studies, in our study, PGC frequency increased gradually with increasing
171 age, with 7% in the 3-6 year age group and 51.6% in the 12-15 year age group, respectively.
172 In our study, the youngest patient with PGC was 5 months old. PGC was observed only in
173 four subjects younger than 3 years. To the best of our knowledge, this is the first time we
174 observed PGC at a very young age using contemporary CT technology. In the previous study,
175 in the majority of patients, PGC morphology was single or punctate (71%).⁴ Similarly, in our
176 study, single or punctate PGC were the most common morphology pattern, with a frequency
177 of 83.51%. The habenula is a bilaterally paired epithalamic nuclear complex situated close to
178 the dorsomedial surface of the thalamus. It plays an important role in the limbic system and
179 acts as a relay and processing center between the midbrain and the limbic system.¹⁷ Its
180 calcifications generally appear as a curvilinear pattern with a prevalence rate of 15% in
181 adults.¹ The composition of these calcifications is found to be similar to that of the pineal
182 gland with salts of calcium and magnesium.¹⁴ In a previous study, habenular calcifications
183 were noted in 10% of subjects younger than 9 years old, and they were the most frequent site
184 of calcification in the epithalamus.⁴ In contrast, we observed habenular calcifications only in
185 4.1% of the patients younger than 9 years of age. However, it increased to 8.9% in subjects
186 aged 9-15 years. An association between habenular calcification and pathophysiology has
187 been postulated as habenular calcifications are observed in schizophrenia patients.¹⁸⁻²⁰ Hence,
188 baseline data of habenular calcifications are clinically important.

189

190 The choroid plexus produces cerebrospinal fluid and helps in the removal of brain metabolic
191 waste and xenobiotics.²¹ It is the major source of transferrin protein in the brain.²² The atria
192 of the lateral ventricles are the most commonly affected sites of calcification, followed by the
193 third or fourth ventricles.¹ Similar to previous studies,^{23,24} in our study, choroid plexus
194 calcification increased significantly with age. In a study by Kendall and Cavanagh, choroid
195 plexus calcification was found in only 2% of subjects younger than 8 years.²⁴ Modic et al.
196 have noted choroid calcification in 0.5% of subjects younger than 10 years old.²⁵ In a study
197 by Doyle and Anderson, it was noted in 7% and 16% of subjects younger than 10 and 16
198 years, respectively.¹⁰ Whitehead et al. have noted the calcification in 12% of children
199 younger than 9 years of age, and the youngest subject was less than 1 month old.⁴ In our
200 study, choroid plexus calcification was the most common intracranial calcification, with a
201 frequency of 35.21%. In subjects less than 9 years of age, it was noted in 35.1% of subjects.
202 The youngest patient with choroid calcification was 4 months old. In the previous study by

203 Whitehead et al., the majority of choroid plexus calcifications were single or punctate
204 (93.1%).⁴ Similarly, in our study, single or punctate choroid plexus calcifications were
205 observed in majority of the subjects (83.51%). Furthermore, choroid calcifications were
206 found bilaterally in majority of the subjects. Various pathological conditions such as
207 intraventricular infection, inflammation, hemorrhage, chronic calcium and phosphate
208 imbalance are known to be associated with premature choroid plexus mineralization. Hence,
209 age thresholds of normally expected choroid plexus calcification are clinically important to
210 distinguish physiology from pathology.⁴

211

212 In children, PICs in falx cerebri and tentorium cerebelli are rare, and is often identified as an
213 incidental finding during routine brain CT examination.²⁶ In the skull radiographs of adults,
214 calcification of falx cerebri was observed in 7% of subjects.^{27,28} In two different CT studies of
215 adults, dural calcifications were observed in 7.3% and 12.5% of subjects,^{5,29} with a male
216 dominance.⁵ To the best of our knowledge, physiological calcifications in the dural folds in
217 children have been reported only in two studies. In a study by Kendall and Cavanagh, dural
218 calcifications were observed in 0.8% of subjects less than 15 years of age.²⁴ In another study
219 by Whitehead et al., it was observed in 1% of subjects less than 9 years of age.⁴ In this study,
220 dural calcifications were most prevalent in tentorium cerebelli followed by falx cerebri.⁴

221

222 In contrast, we observed 5.86% in falx cerebri and 3.04% in tentorium cerebelli. Furthermore,
223 falx cerebri and tentorium cerebelli calcifications are not present in less than 2 and 7 years,
224 respectively. As falx cerebri is formed from pluripotent embryonic mesenchymal stem cells,
225 any external stimuli including, irritation, trauma, and haemorrhage would predispose these
226 mesenchymal cells to transform into osteogenic cells, resulting in calcification.^{30,31} The
227 extensive dural calcifications are known to be associated with a few pathological conditions,
228 particularly basal cell nevus syndrome.³² There is inconsistency in the existing literature
229 regarding gender influence on the occurrence of PICs in the paediatric population. In a study
230 by Whitehead et al., no significant gender difference ($p=0.41$) was observed.⁴ Two other
231 studies by Doyle & Anderson¹⁰ and Caliskan and Ozturk³, found no evidence of a gender
232 effect on PGC calcification. Similarly, in the present study, gender influence on intracranial
233 calcification was not observed. In contrast, two studies have reported a significant gender
234 influence with male dominance.^{5,29} Further research needs to be conducted to draw a
235 conclusive result in this regard. The prior knowledge of reference values of PICs in children
236 is clinically important as this may frequently interfere with the differential diagnosis of

237 metabolic mineralization, intracranial hemorrhage, and tumours. The following are some of
238 the limitations of this study. The volume, or CT density of PIC could not be performed. The
239 study sample may not be representative of the Omani population because it is a single-
240 centered study. A multi-centered study involving subjects from various parts of Oman and
241 analysis of calcification quantification would be interesting.

242

243 **Conclusion**

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

251

252 **Conflicts of interest**

253 The authors declare that they have no conflict of interest

254

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257

258 **Author Contributions**

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

265

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270

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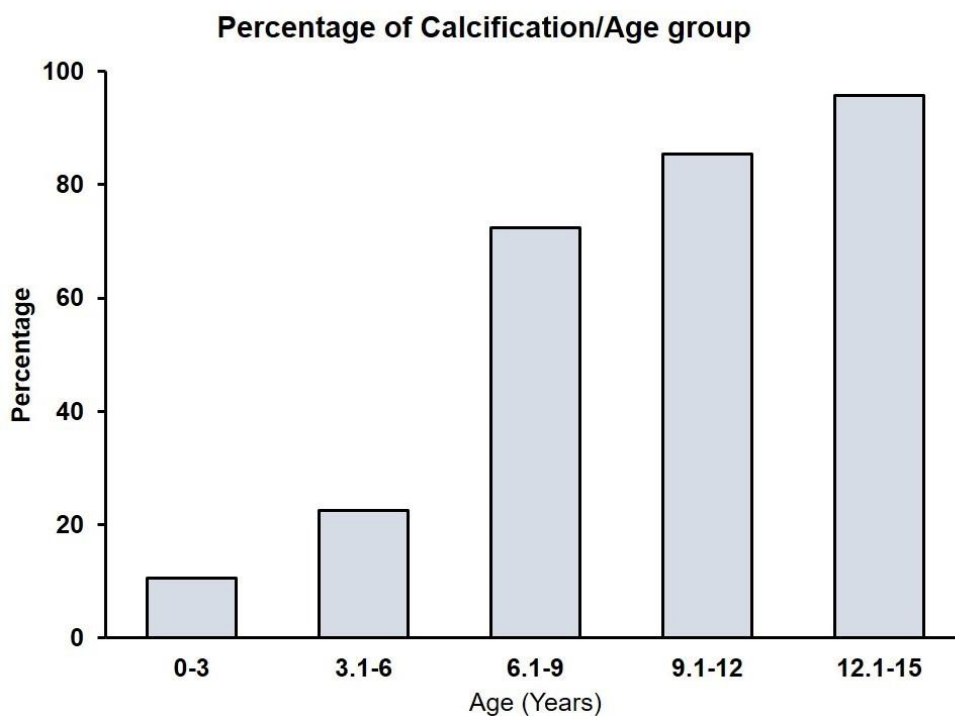
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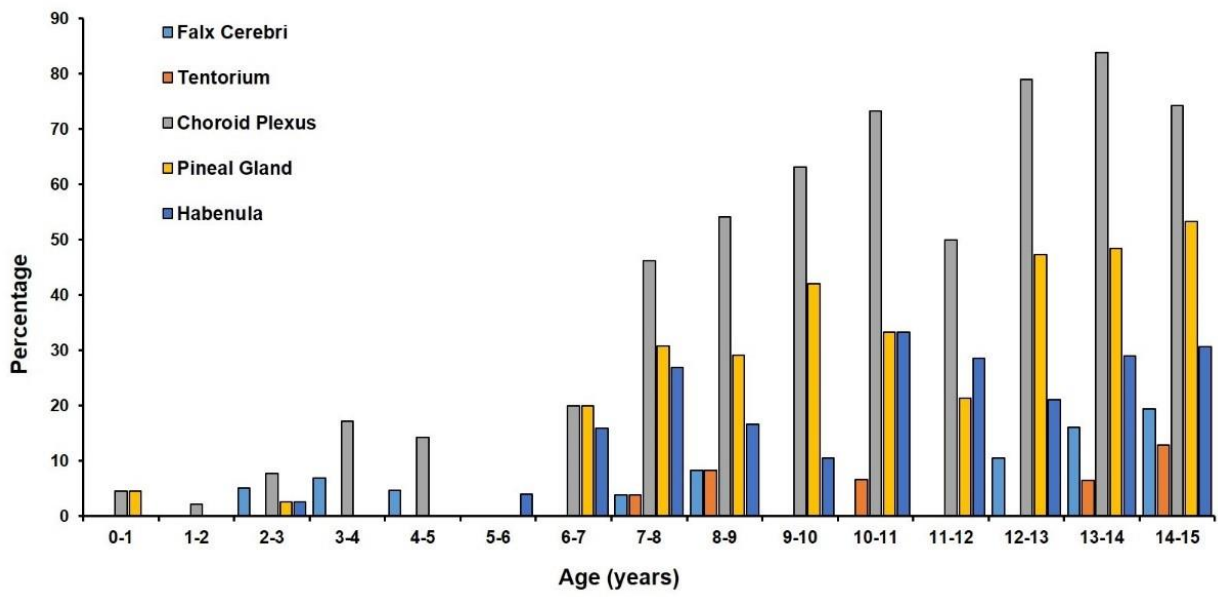
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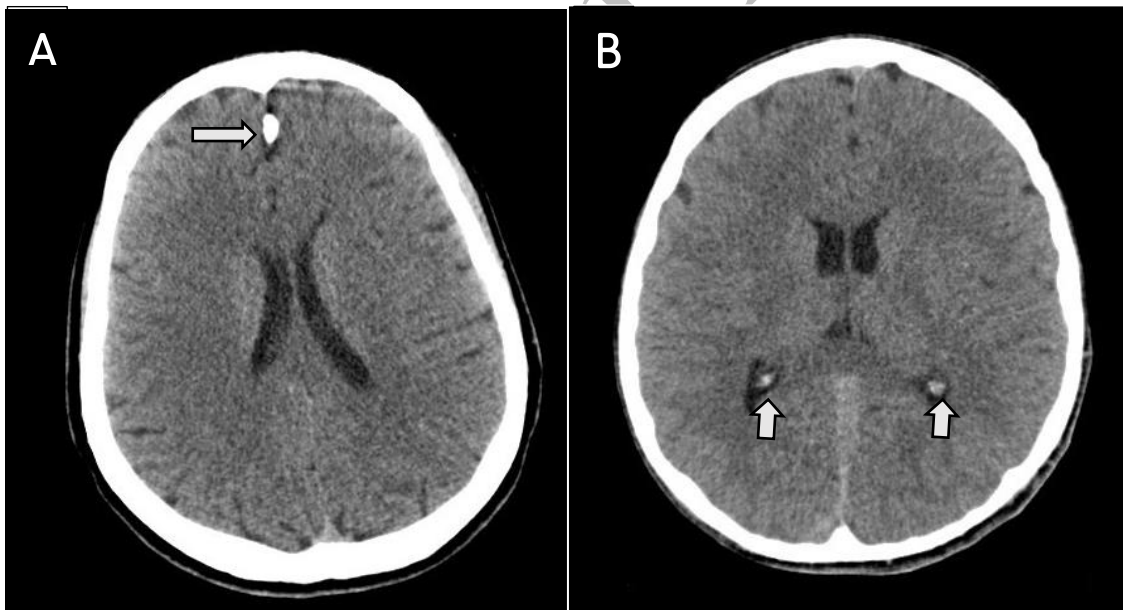
355
 356 **Figure 1.** The frequency of physiological intracranial calcification in different age groups. The
 357 total number of patients analyzed was 460. Note calcification increased with increasing age
 358 (Chi square test; $p < 0.01$).



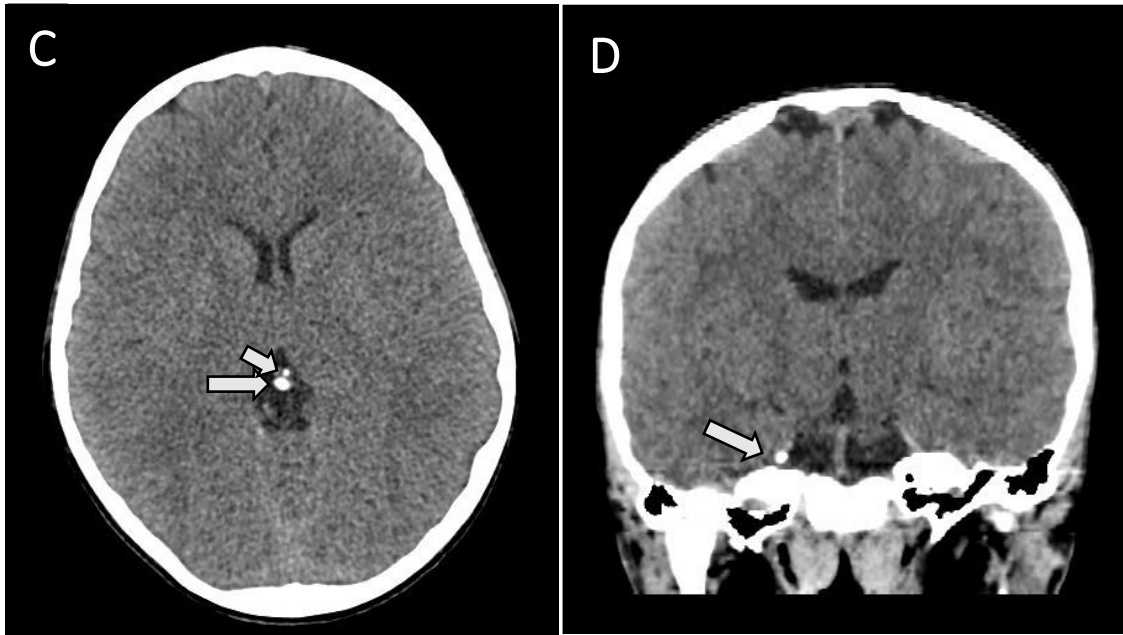
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361 **Figure 2:** The frequency of physiological intracranial calcifications among the 460 patients
 362 across different ages.

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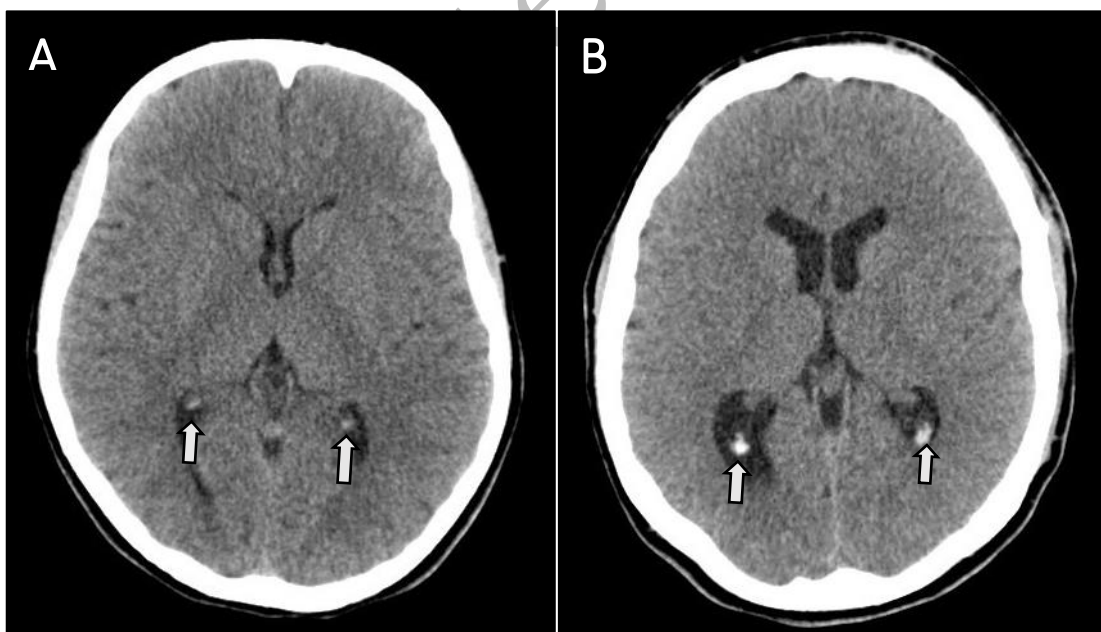
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Figure 3. Examples of intracranial calcifications from the study. Axial CT images of the brain show (A) focal calcification in the falx (arrow), (B) bilateral calcifications of the choroid plexus in the trigones of the lateral ventricles (arrows),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



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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).

377 **Table 1.** The age ranges of physiological intracranial calcifications at different regions of brain.

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

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