

Association between Foramen Size and Febrile Seizure Status in the Pediatric Population: A Two-Center Retrospective Analysis

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Abstract

Objective Febrile seizures have been shown to occur in 2 to 5% of children between the ages of 6 months and 5 years, making them the most common seizures of childhood. Multiple risk factors for febrile seizures have been identified; however, no investigation has been conducted to explore foramen size and associated venous drainage as a potential risk factor for experiencing febrile seizures. Of particular interest are the parietal foramen and the condylar canal, which conduct the parietal emissary vein and the occipital emissary vein, respectively. Emissary veins lack valves, allowing them to play a crucial role in selective brain cooling via a bidirectional flow of blood from the head's evaporating surface. Narrowed cranial apertures conducting these veins may lead to reduced cerebral venous outflow and delayed brain cooling, creating favorable conditions for a febrile event. This study seeks to explore the association between cranial aperture area and febrile seizure status.

Methods A retrospective cross-sectional medical record review study from January 2011 to December 2017 was conducted at a 500-bed academic hospital and a 977-bed private hospital in Lubbock, Texas, United States. A total of 101 complex febrile seizure patients were compared with a similarly aged group of 75 trauma patients representing the normal population. Parietal foramen area and condylar canal area were electronically measured and defined as having “normal” or “below normal” area.

Statistical Analysis Independent *t*-tests were used to compare foramen and canal areas by febrile seizure status. Logistic regression analyses were conducted to determine the association of small cranial aperture area with febrile seizure status.

Results Below normal parietal foramen area had a strong association with febrile seizures in our patient population. Male sex, white race, and complete vaccination status were also found to have significant associations with febrile seizure status.

Conclusion Our findings indicated that narrowed parietal foramen may be considered as a risk factor for febrile seizure development.

Keywords

- ▶ cerebral blood flow
- ▶ febrile seizures
- ▶ neuroanatomy
- ▶ neuroimaging
- ▶ pediatrics
- ▶ risk factors

Introduction

Febrile seizures are an acute neurological condition in children. With a 2 to 5% occurrence rate, they are the most common form of childhood seizure and account for a large portion of emergency department visits each year.^{1–4} The American

Academy of Pediatrics (AAP) defines a febrile seizure as “a seizure accompanied by a fever (temperature >100.4°F or 38°C by any method), without central nervous system infection, that occurs in infants and children at the age of 6 to 60 months.”⁵ Febrile seizures may be classified as simple or complex based on duration, nature, and rate of occurrence.^{1–4,6} Whereas



simple febrile seizures are generalized in nature and have a brief duration with no recurrence—complex febrile seizures are longer—may be accompanied by focal symptoms and can recur within 24 hours.^{1-4,6,7} Current risk factors for febrile seizures include age, male sex, vaccination status, nutritional deficiencies, family history, duration of initial seizure, developmental delay, and temperature.^{1-4,6-9} Since the pathogenesis of febrile seizures involves elevated body temperature,^{1-4,7} an investigation into the relationship between cooling mechanisms of the brain—emissary veins and their respective canals—and occurrence of febrile seizure is warranted.

In a hyperthermic state, blood in the emissary veins flows into the skull (opposite the direction of normal venous outflow), allowing cooler blood to reduce elevated brain temperatures.¹⁰ We predicted that narrowed areas of the associated canals—specifically the condylar canals and the parietal foramina—could prevent sufficient blood flow from reaching the brain, predisposing an individual to febrile seizures. Here, we investigated the relationship between the areas of these regions as measured by computed tomography (CT) imaging with the occurrence of complex febrile seizures in a pediatric cohort.

Methods

Patient Selection

This retrospective study had institutional review board approval with a waiver of the informed consent requirement. We isolated a group of 552 patients who were diagnosed as having a febrile seizure (simple or complex) at either University Medical Center (UMC) or Covenant Medical Center (CMC) in Lubbock, Texas, United States, between January 2011 and December 2017. Febrile seizure cases were identified by International Statistical Classification (ICD)-9 (780.31–780.32) and ICD-10 (R56.00–R56.01) codes. From these cases, patients between the ages of 6 and 60 months at diagnosis were selected for our initial cohort (in accordance with the AAP febrile seizure definition⁵). The patients' MRN number was then replaced with generic numerical substitutes (1, 2, 3, etc.) for declassification. Subjects were excluded if they had prior neurosurgical intervention, preexisting neurologic or cranial structural anomalies, prior diagnosis of nonfebrile epileptic activity, coexisting diagnoses of febrile seizure and injury due to external causes, or were current recipients of antiepileptic or known epileptogenic medications.

Though our initial cohort included both simple and complex febrile seizure diagnoses, we found neuroimaging to be available for only the complex febrile seizure subgroup. We then narrowed our cohort to include just complex febrile seizure diagnoses. For subjects with more than one encounter, data were only collected for the most recent encounter meeting study eligibility criteria.

Measurements

The following demographic/categorical data were collected: age, sex, race/ethnicity, and ICD-9 and ICD-10 codes. The patient's head circumference, head circumference percentile, and presence of any previously mentioned known risk factors

for febrile seizures—male sex, vaccination status, nutritional deficiencies, family history, and developmental delay—were also documented.⁷⁻⁹ We then measured the parietal foramina and condylar canal dimensions from this group of patients through the use of electronic calipers and the freehand analysis tool on head CT imaging software. Measurements were repeated three times for each foramen or canal visualized on imaging software (left only, right only, or bilateral), and the average of these values was taken as a single, final value for each canal/foramen area.

Classification

Since we were interested in the possibility of a correlation between reduced canal/foramina area and increased febrile seizure occurrence, both canal and foramen areas were classified as “below normal range” or “within normal range” for each patient. There is much discrepancy in the literature regarding a normal range for these values due to widely accepted anatomical variations in both cranial apertures. Studies have found the condylar canals to have a mean 3.5 mm diameter,¹¹ but little has been discussed with regard to mean area. The parietal foramen have been suggested to have an average diameter of 0.5 mm with greater than 1.5 mm being rare.¹² Others described parietal foramina exceeding 5 mm in diameter as enlarged.¹³ The parietal foramen may also be influenced by sexual dimorphism, as females skulls have been found to have parietal foramina twice as large as their male counterparts (3 mm in females and 1.5 mm in males).^{14,15} A similar trend has not been exhibited in condylar canal measurements. We elected to use the mean areas and standard deviations as described by Wysocki et al, which found a mean area of $12.61 \pm 8.97 \text{ mm}^2$ for the condylar canals and $2.03 \pm 1.24 \text{ mm}^2$ for the parietal foramen.¹⁵ Values that fell within these ranges were classified as “normal,” whereas values that fell below the lower end of this range (3.64 and 0.79 mm^2 for the condylar canals and parietal foramen, respectively) were classified as “below normal.”

Trauma Control Group

The same information and measurements as detailed in the “measurements” and “classification” sections were collected for a group of 75 similarly aged patients seen in the UMC or CMC emergency departments over the same time period. These patients were initially assessed for trauma but found to have no trauma-induced anatomical skull deformities on neuroimaging. Patients were excluded from this cohort if they had experienced any prior neurosurgical intervention, had preexisting neurologic or cranial structural anomalies, or been diagnosed with a febrile seizure. This group represented the normal population and was used as a control group for the purposes of this study.

Statistical Analysis

Independent *t*-tests were used to compare foramen and canal areas by febrile seizure status. Logistic regression analyses were used to estimate multivariate (adjusted) odds ratios with 95% confidence intervals for all categorical variables

(sex, vaccination status, race, family history of seizure, and foramen/canal size categories) in the model.

Results

Of the 552 patients who fit our initial inclusion criteria, 451 were excluded due to lack of head CT imaging or inadequate image quality from patient movement. Of the 329 trauma patients who fit the control group inclusion criteria, 254 were excluded for similar reasons. The mean age of the 101 remaining febrile seizure patients (32 females and 69 males) was 21 months, and the mean age of the 75 remaining trauma patients (40 females and 35 males) was 38 months. Categorical characteristics and presence of known risk factors for febrile seizures are listed in ►Table 1.

Classification of foramen and condylar canal size in our patient population is listed in ►Table 2. Of the 101 febrile

seizure patients included in this study, 70 patients (69.3%) fit the criteria for below normal parietal foramen area, compared with 30 of the 75 trauma patients (40.0%; positive predictive value = 70%). Additionally, 9 of the 101 febrile seizure patients (8.9%) and no trauma patients were classified as having below normal condylar canal area. Average foramen and canal areas by febrile seizure status are shown in ►Fig. 1. Comparisons of condylar canals and of parietal foramina (illustrated by yellow arrows on images) are shown in ►Figs. 2 and 3, respectively.

Adjusted odds ratios with 95% confidence intervals are shown in ►Fig. 4 and ►Table 3. Male sex ($p = 0.016$), white race ($p < 0.001$), complete vaccination status ($p = 0.003$), and presence of a below normal parietal foramen area ($p = 0.015$) were significantly associated with the development of febrile seizures. Having a family history of febrile seizures ($p = 0.082$) and below normal condylar canal area ($p = 0.207$) were not found to have significant associations. Head circumference,

Table 1 Sample characteristics of patients by febrile seizure status

	Overall, % (number of patients)	Trauma, % (number of patients)	Febrile seizure, % (number of patients)	p-Value
Age in mo (range)	24 (16–48)	38 (23–60)	21 (14–32)	<0.0001
Sex				0.004
Female	40.9 (72)	22.7 (40)	18.2 (32)	
Male	59.1 (104)	19.9 (35)	39.2 (69)	
Race				<0.0001
White	34.0 (55)	21.6 (35)	12.4 (20)	
Hispanic	66.1 (107)	20.4 (33)	45.7 (74)	
Recurrent febrile seizure				<0.0001
No	68.8 (121)	42.6 (75)	26.1 (46)	
Yes	31.3 (55)	0 (0)	31.3 (55)	
Vaccination				<0.0001
No	10.8 (19)	8.5 (15)	2.3 (4)	
Yes	89.2 (157)	34.1 (60)	55.1 (97)	
Family history of seizures				0.001
No	82.4 (145)	39.8 (70)	42.6 (75)	
Yes	17.6 (31)	2.8 (5)	14.8 (26)	
Developmental delay				0.103
No	84.7 (149)	34.1 (60)	50.6 (89)	
Yes	15.3 (27)	8.5 (15)	6.8 (12)	

Table 2 Classification of parietal foramen and condylar canal size of patients by febrile seizure status

	Overall, % (number of patients)	Trauma, % (number of patients)	Febrile seizure, % (number of patients)	p-Value
Parietal foramen size				<0.0001
Below normal	56.8 (100)	17.1 (30)	39.8 (70)	
Normal	43.2 (76)	25.6 (45)	17.6 (31)	
Condylar canal size				0.003
Below normal	86.4 (152)	33.0 (58)	53.4 (94)	
Normal	13.6 (24)	9.7 (17)	4.0 (7)	

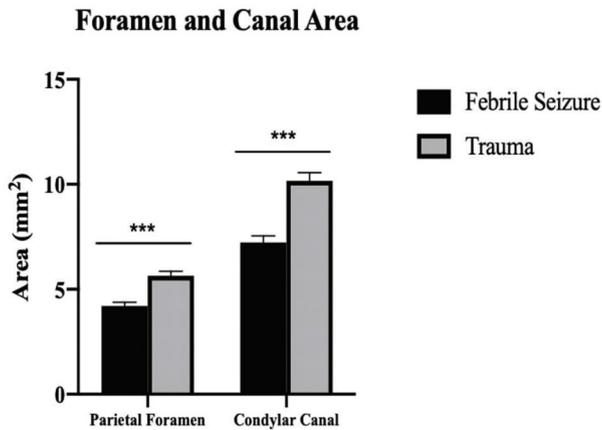


Fig. 1 Parietal foramen and condylar canal area by febrile seizure status. Significant differences were found between febrile seizure patients and trauma patients representing a normal population for both parietal foramen and condylar canal area; *** $p < 0.001$.

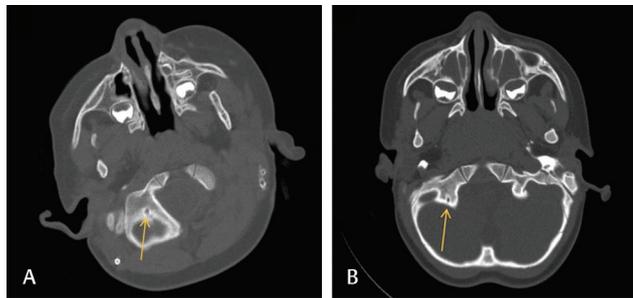


Fig. 2 Comparison of normal (A) and below normal (B) condylar canals on head CT imaging. (A) Head CT of a patient in the nonfebrile seizure trauma group used to illustrate a condylar canal that fit our criteria for normal size (12.57 mm² shown here). (B) Head CT of a patient in the febrile seizure group used to illustrate a below normal condylar canal size (2.63 mm² shown here). CT, computed tomography.

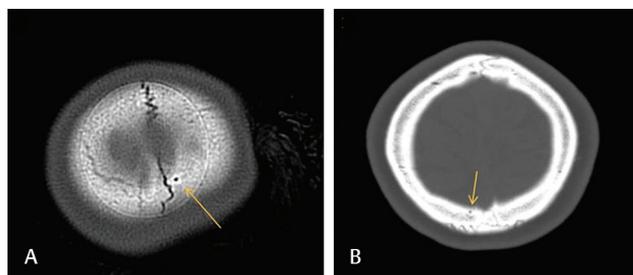


Fig. 3 Comparison of normal (A) and below normal (B) parietal foramina on head CT imaging. (A) Head CT of a patient in the nonfebrile seizure trauma group used to illustrate a parietal foramen that fit our criteria for normal size (2.80 mm² shown here). (B) Head CT of a patient in the febrile seizure group used to illustrate a below normal parietal foramen size (0.74 mm² shown here). CT, computed tomography.

head circumference percentile, nutritional deficiencies, and developmental delay were excluded from analysis due to incomplete documentation in multiple patients' medical records.

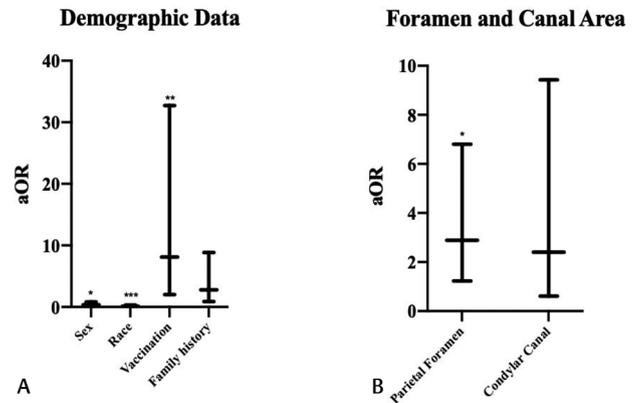


Fig. 4 Adjusted odds ratios by febrile seizure status (A, B). We used the following criteria as reference data: male sex, white race, incomplete vaccinations, no family history of febrile seizure, normal parietal foramen area, and normal condylar canal area. Using this model, male sex, white race, complete vaccination status, and presence of a below normal parietal foramen area were significantly associated with the development of febrile seizures; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Discussion

Male sex, complete vaccination status, white race, and below normal parietal foramen area were significantly associated with the occurrence of febrile seizures in our patient population.

Although some studies have not shown a clear sex predilection for the occurrence of febrile seizures,^{2,6} this study demonstrated a significant association between male sex and febrile seizures. Other literature reports males to have a higher frequency of febrile seizures,^{3,16-19} which is more consistent with our findings. This may be attributed to sexual dimorphism in parietal ossification, as males have been shown to have smaller average parietal foramen sizes than females.^{14,15}

The significant association between vaccination status and febrile seizure occurrence that is demonstrated in this study has been well documented in the literature.^{2,3,7,20} Although vaccine-induced febrile seizures do not lead to deleterious outcomes, they are the second most common medical event associated with the condition.^{3,20} None of the standard vaccinations are currently contraindicated in patients with febrile seizures.²⁰⁻²²

As for the significance of race and febrile seizure development, the literature reports a lower incidence of febrile seizures within the white race relative to Asian populations (3–5% in whites vs. 8–10% in Asians).^{2,3,6} However, a limitation of this study is the predominately white and Hispanic demographic within our sample, which limits generalizability to other racial/ethnic groups. It has been shown that Hispanic children have lower odds of being severely affected by febrile seizures than white children²³; however, another study found increased incidence of febrile seizures in Hispanic versus non-Hispanic populations but no significance between race and febrile seizure duration.²⁴

Table 3 Adjusted odds ratios by febrile seizure status

	Adjusted odds ratio	95% confidence interval	p-Value
Sex			
Male (reference)			
Female	0.35	(0.15–0.82)	0.016
Race			
White (reference)			
Hispanic	0.13	(0.05–0.33)	<0.001
Vaccination status			
Incomplete (reference)			
Complete	8.12	(2.01–32.73)	0.003
Family history of seizure			
No (reference)			
Yes	2.79	(0.87–8.85)	0.082
Parietal foramen area			
Normal (reference)			
Below normal	2.89	(1.23–6.80)	0.015
Condylar canal area			
Normal (reference)			
Below normal	2.40	(0.61–9.43)	0.207

The mean age of patients who experienced febrile seizures within this study is 21 months, which is also in accordance with ages reported in the literature—reported febrile seizures occur between 3 months and 5 years of age,^{1–4,7} with a peak age between 18 and 24 months.^{1–3,6}

Many studies have argued against the use of neuroimaging for first-time simple febrile seizures.^{1–3,7,25} The predominant argument opposing CT scanning is the escalating future cancer risk due to radiation exposure.^{3,7,25} The incidence of a clinically significant CT abnormality in complex febrile seizure patients has been reported to be as low as 1.6 to 5.0%.^{26,27} Teng et al found that in 71 patients experiencing a first complex febrile seizure—none required emergency neurosurgical or medical intervention—indicating that neuroimaging posed an unnecessary risk.^{7,28} However, current guidelines state that neuroimaging may be considered in febrile seizure patients presenting with neurologic abnormalities or in those with recurrent febrile seizures.^{2,3,7} If previously existing neuroimaging is available for such patients, a repeated examination of parietal foramen that reveals a small foramen area may be considered as a possible pathologic cause. Future replication of these results in cohorts with differing population characteristics is needed to further support the validity of foramen size as a risk factor for febrile seizure development.

Conclusion

Below normal parietal foramen area is significantly associated with febrile seizure development in our patient population. Our findings suggested that larger multicenter retrospective analyses may be necessary in febrile seizure patients with

prior neuroimaging (related or unrelated) before considering any changes to febrile seizure management protocols.

Note

This study was approved by the Institutional Review Board.

Conflict of Interest

None declared.

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References

- 1 Patterson JL, Carapetian SA, Hageman JR, Kelley KR. Febrile seizures. *Pediatr Ann* 2013;42(12):249–254
- 2 Gupta A. Febrile seizures. *Continuum (Minneapolis)* 2016;22(1 Epilepsy):51–59
- 3 Chung S. Febrile seizures. *Korean J Pediatr* 2014;57(9):384–395
- 4 Mewasingh LD. Febrile seizures. *BMJ Clin Evid* 2014;2014 pii: 0324
- 5 Dougherty D, Duffner PK, Baumann RJ, et al. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. *Pediatrics* 2008;121(6):1281–1286
- 6 Shellhaas RA, Camfield CS, Camfield PR. Febrile Seizures. In: Aminoff MJ and Daroff RB eds. *Encyclopedia of The Neurological Sciences (Second Edition)*. Academic Press; 2014:281–282
- 7 Graves RC, Oehler K, Tingle LE. Febrile seizures: risks, evaluation, and prognosis. *Am Fam Physician* 2012;85(2):149–153
- 8 Berg AT, Shinnar S, Shapiro ED, Salomon ME, Crain EF, Hauser WA. Risk factors for a first febrile seizure: a matched case-control study. *Epilepsia* 1995;36(4):334–341

- 9 Bethune P, Gordon K, Dooley J, Camfield C, Camfield P. Which child will have a febrile seizure? *Am J Dis Child* 1993;147(1):35–39
- 10 Kunz AR, Iliadis C. Hominid evolution of the arteriovenous system through the cranial base and its relevance for craniosynostosis. *Childs Nerv Syst* 2007;23(12):1367–1377
- 11 Matsushima K, Kawashima M, Matsushima T, Hiraiishi T, Noguchi T, Kuraoka A. Posterior condylar canals and posterior condylar emissary veins—a microsurgical and CT anatomical study. *Neurosurg Rev* 2014;37(1):115–126
- 12 Boyd BG, *J Anat* 1930; 65(Pt 1): 108–121
- 13 Pířová H, Rangel de Lázaro G, Velemínský P, Bruner E. Craniovascular traits in anthropology and evolution: from bones to vessels. *J Anthropol Sci* 2017;95:35–65
- 14 Freire AR, Rossi AC, de Oliveira VCS, Prado FB, Caria PHF, Botacin PR. Emissary foramina of the human skull: anatomical characteristics and its relations with clinical neurosurgery. *Int J Morphol* 2013;31(1):287–292
- 15 Wysocki J, Reymond J, Skarzyński H, Wróbel B. The size of selected human skull foramina in relation to skull capacity. *Folia Morphol (Warsz)* 2006;65(4):301–308
- 16 Farwell JR, Blackner G, Sulzbacher S, Adelman L, Voeller M. First febrile seizures. Characteristics of the child, the seizure, and the illness. *Clin Pediatr (Phila)* 1994;33(5):263–267
- 17 Esmaili Gourabi H, Bidabadi E, Cheraghalipour F, Aarabi Y, Salamat F. Febrile seizure: demographic features and causative factors. *Iran J Child Neurol* 2012;6(4):33–37
- 18 Habib Z, Akram S, Ibrahim S, Hasan B. Febrile seizures: factors affecting risk of recurrence in Pakistani children presenting at the Aga Khan University Hospital. *J Pak Med Assoc* 2003;53(1):11–17
- 19 Mahyar A, Ayazi P, Fallahi M, Javadi A. Risk factors of the first febrile seizures in Iranian children. *Int J Pediatr* 2010;2010:862897
- 20 Principi N, Esposito S. Vaccines and febrile seizures. *Expert Rev Vaccines* 2013;12(8):885–892
- 21 Li X, Lin Y, Yao G, Wang Y. The influence of vaccine on febrile seizure. *Curr Neuropharmacol* 2018;16(1):59–65
- 22 Sawyer MH, Simon G, Byington C. Vaccines and febrile seizures: quantifying the risk. *Pediatrics* 2016;138(1):e20160976
- 23 Okubo Y, Handa A. National trend survey of hospitalized patients with febrile seizure in the United States. *Seizure* 2017;50:160–165
- 24 Hesdorffer DC, Benn EKT, Bagiella E, et al; FEBSTAT Study Team. Distribution of febrile seizure duration and associations with development. *Ann Neurol* 2011;70(1):93–100
- 25 The American Academy of Pediatrics. Febrile seizures: guideline for the neurodiagnostic evaluation of the child with a simple febrile seizure. *Pediatrics* 2011;10.1542/peds.2010-3318
- 26 Rasool A, Choh SA, Wani NA, Ahmad SM, Iqbal Q. Role of electroencephalogram and neuroimaging in first onset afebrile and complex febrile seizures in children from Kashmir. *J Pediatr Neurosci* 2012;7(1):9–15
- 27 McAbee GN, Barasch ES, Kurfist LA. Results of computed tomography in “neurologically normal” children after initial onset of seizures. *Pediatr Neurol* 1989;5(2):102–106
- 28 Teng D, Dayan P, Tyler S, et al. Risk of intracranial pathologic conditions requiring emergency intervention after a first complex febrile seizure episode among children. *Pediatrics* 2006;117(2):304–308