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Metabolic disturbances in the first seizure with fever: Study of children in Thai hospital

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Background : *Seizure with fever is a common neurological manifestation in children, the most common cause of which is febrile seizure. In almost all cases, clinical practice includes laboratory investigation. In spite of multiple studies, no evidence suggests routine blood studies improve pediatric diagnosis.*

Objective : *Determine association between metabolic disturbances and the first seizure with fever in children.*

Methods : *Retrospective descriptive study consisting of review of children admitted with first seizure with fever, 3 months to 6 years, from January 1, 2012 to December 31, 2016. Demographics and clinical data, etiology of fever, characteristics of seizure, metabolic laboratory investigations and cerebrospinal fluid profiles were collected. Statistical significance was set at $P < 0.05$.*

Results : *The study included 319 children, median age 1.3 years (range 0.17 to 5.83 years). Respiratory tract infection (58%) was the most common etiology of fever. Abnormal laboratory results included anemia for age (25.1%), hyponatremia (24.7%), hypocalcemia (2.3%) and metabolic acidosis (88.1%). Complex febrile seizure was found in 53 cases (16.7%).*

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Comparing simple febrile seizure with complex febrile seizure, statistical significance between the two groups was found only with respect to delayed development and family history of febrile seizure or epilepsy in first degree relatives. Age, sex, duration of seizure, and metabolic laboratory test results were not significantly different between these two groups.

Conclusion : *The level of metabolic disturbance was not significantly associated with the febrile seizure. As a result of this study, laboratory investigations are no longer recommended for all patients, except in the presence of clinically suspicious factors.*

Keywords : *First episode seizure, febrile seizure, fever, metabolic disturbance.*

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เหตุผลของการทำวิจัย : *อาการชักร่วมกับมีไข้สูงเป็นอาการแสดงทางระบบประสาทในเด็กที่พบได้บ่อย สาเหตุโดยมากเป็นจากภาวะชักจากไข้ สำหรับการส่งตรวจทางห้องปฏิบัติการการในทางเวชปฏิบัติแล้ว พบว่ามีการส่งตรวจในผู้ป่วยทุกคน แม้ว่าได้มีงานวิจัยออกมารองรับว่าการส่งตรวจทางห้องปฏิบัติการ ไม่มีความจำเป็นที่ต้องส่งในเด็กทุกคนที่มาด้วยอาการไข้และชักก็ตาม*

วัตถุประสงค์ : *เพื่อศึกษาถึงภาวะผิดปกติทางเมตาบอลิกในเด็กที่มาด้วยอาการไข้และชักครั้งแรก*

วิธีการทำวิจัย : *เป็นการศึกษาเชิงพรรณนาย้อนหลัง จากเวชระเบียนผู้ป่วยที่ได้รับการวินิจฉัยว่ามีภาวะไข้ และชักครั้งแรก อายุตั้งแต่ 3 เดือนถึง 6 ปี ที่เข้ารับการรักษาในโรงพยาบาลภูมิพลอดุลยเดช ตั้งแต่วันที่ 1 มกราคม พ.ศ. 2555 – 31 ธันวาคม พ.ศ. 2559 ได้แก่ ข้อมูลพื้นฐานทั่วไป อาการ สาเหตุของไข้ ลักษณะชัก ผลตรวจทางห้องปฏิบัติการ และผลตรวจน้ำไขสันหลัง*

ผลการศึกษา : *ผู้ป่วยที่มีอาการไข้ และชักครั้งแรกทั้งหมด 319 ราย มีอายุเฉลี่ย 1.33 ปี (0.17-5.83 ปี) โดยสาเหตุของไข้ที่พบมากที่สุดเกิดจากการติดเชื้อทางเดินหายใจ (ร้อยละ 58) ในการส่งตรวจทางห้องปฏิบัติการ พบภาวะซีดตามเกณฑ์อายุร้อยละ 25.1 พบระดับโซเดียม และแคลเซียมในเลือดต่ำร้อยละ 24.7 และ 2.3 ตามลำดับ และพบภาวะเลือดเป็นกรดร้อยละ 88.1 พบภาวะชักจากไข้ชนิดซับซ้อน 53 ราย (ร้อยละ 16.7) เมื่อศึกษาความสัมพันธ์ระหว่างภาวะชักจากไข้และภาวะชักจากไข้ชนิดซับซ้อนพบว่าภาวะพัฒนาการช้า และการมีประวัติคนในครอบครัวเป็นภาวะชักจากไข้และลมชัก มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ และพบว่าอายุ เพศ ระยะเวลาในการชัก และผลตรวจทางห้อง ปฏิบัติการระหว่างสองกลุ่ม ไม่มีความแตกต่างกันอย่างมีนัยสำคัญ*

สรุป : *ความผิดปกติทางเมตาบอลิกไม่มีความสัมพันธ์กับภาวะชักจากไข้ในเด็กที่มาด้วยไข้ และชักครั้งแรก จึงไม่แนะนำให้มีการตรวจทางห้องปฏิบัติการในผู้ป่วยทุกคน ยกเว้นมีข้อบ่งชี้ในการส่งตรวจ*

คำสำคัญ : *ไข้ชัก, ภาวะชักจากไข้, ภาวะเกลือแร่ผิดปกติ, การส่งตรวจทางห้องปฏิบัติการ.*

Seizure with fever is the most commonly manifested neurological dysfunction in children. [1, 2] The most common convulsive event is febrile seizure (FS) which occurs in 2 - 5% of the general population.[1, 2] Febrile seizures occur between 3 and 60 months of age and are associated with fever but there is no evidence of intracranial infection or other definable cause. [1, 2]

In general, a simple febrile seizure does not usually require further evaluation, specifically electroencephalograms (EEGs), blood studies, or neuroimaging. [1] The specific guidelines for the neurological diagnostic evaluation of the child with a simple FS were published by the American Academy of Pediatrics (AAP) in 2011. [1] It is recommended that the cause of the child's fever be identified. Meningitis should be considered in the differential diagnosis for any febrile child and lumbar puncture should be performed if the child has ill appearance or otherwise exhibit clinical signs or symptoms. A lumbar puncture is an option in a child 6 to 12 months of age who lacks *Haemophilus influenza type b (Hib)* or *Streptococcus pneumonia* immunizations or for whom immunization status is unknown. It is also an option in children who have been pretreated with antibiotics.

There is no national consensus or policy on routine laboratory evaluations and lumbar punctures in infants and children presenting with seizures during a febrile illness. This study includes a review to history, clinical evaluation, and laboratory testing of hematological, biochemical and cerebrospinal fluid in children who presented with fever and seizure at Bhumibol Adulyadej Hospital.

Materials and Methods

Subjects

The medical records of children, aged 3 months to 6 years old, who were diagnosed as with first seizure and fever and admitted to Bhumibol Adulyadej Hospital from January 1, 2012 to December 31, 2016, were analyzed. The data included age, gender, family history, development, characteristics and duration of seizure, etiology of fever, vital signs, degree of dehydration, result of complete blood count (CBC), serum sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, blood sugar, blood urea nitrogen (BUN), creatinine (Cr), urine analysis (UA) and result of lumbar puncture.

Clinical and laboratory definition

Febrile seizure was divided into 2 groups, simple and complex FS. Simple FS is defined as primary generalized seizure that lasts for less than fifteen minutes and does not reoccur within 24 hours, and complex FS as focal, prolonged more than 15 minutes and/or recurrent within 24 hours. [1, 2]

Hyponatremia is defined as mild, moderate or severe if sodium level between 130 - 134, 125 - 129, or less than 125 mmol/L, respectively. Hypernatremia is defined as sodium level greater than 145 mmol/l. In some cases, other electrolytes were measured. Hypocalcemia is defined as calcium less than 8.8 mg/dL, hypomagnesaemia is magnesium level less than 1.5 mg/dL, hypoglycemia is blood sugar less than 40 mg%, and hyperglycemia is greater than 200 mg%. Metabolic acidosis is defined as bicarbonate level less than 20 mmol/L.

Abnormal complete blood count results were defined as anemia for age if hemoglobin less than 11

mg/dL in age of 3 month to 5 years old and 11.5 mg/dL in age of 5 to 6 years old. Leukocytosis is defined as white blood cell counts were more than 15×10^3 / mm^3. Band form of neutrophils is defined as band form shown in CBC.

Abnormal cerebrospinal fluid (CSF) results are defined as the presence of one or more of the following: white blood cell greater than 5/mm^3, CSF/blood glucose ratio less than 0.6, protein greater than 50 mg/dL, and positive Gram stain and culture. [3 - 5]

Sample size and statistical analysis

The sample size of the study was 319 children. Data were analyzed with SPSS version 19. Descriptive analysis was performed using frequency, percentage, mean, and standard deviation. Chi-square or Fisher's exact test and the independent *t*-test were used to analyze categorical and continuous variables, respectively. Statistical significance was set at the $P < 0.05$.

Results

Demographic data is shown in Table 1. Of the 319 children, 311 (97.5%) were Thai and 182 (57.1%) were boy. The median age was 1.33 years (range 0.17 to 5.83 years). The median length of stay was 4 days (range 1 to 73 days).

Table 1. Demographic data of 319 patients with 1st episode seizure with fever.

Characteristic	N (%)
Sex	
Male	182 (57.1)
Age (years)	
Range	0.17-5.83
(Median)	(1.33)
Nationality	
Thai	311 (97.5)
Other	8 (2.5)
Type of seizure	
Focal seizure	3 (0.9)
GTC	170 (53.3)
Generalized tonic seizure	145 (45.5)
Diagnosis	
Simple febrile seizure	265 (83.1)
Complex febrile seizure	53 (16.6)
Viral meningitis	1 (0.3)
Status epilepticus	2 (0.6)
Delayed development	10 (3.1)
Family History	
Febrile seizure	73 (22.9)
Epilepsy	3 (0.9)

Table 1. (Con) Demographic data of 319 patients with 1st episode seizure with fever.

Characteristic	N (%)
Degree of dehydration	
Mild dehydration	128 (40.1)
Moderate dehydration	21 (6.6)
Etiology of fever	
Respiratory tract infection	185 (58)
Acute gastroenteritis	48 (15)
Viral exanthem	23 (7.2)
Viral infection	16 (5)
Post vaccination	13 (4.1)
Urinary tract infection	11 (3.4)
Dengue infection	2 (0.6)
Meningitis/Encephalitis	1 (0.3)
Others cause	20 (6.3)

Of the subject children, 316 (99.1%) presented with acute fever less than 7 days before seizure, and 282 (88.4%) presented with fever less than 12 hours before. The most common type of seizure was generalized tonic-clonic (52.7%). Simple febrile seizure was diagnosed in 265 children (83.1%). The seizure duration ranged from 0.17 minutes to 30 minutes with a median of 2 minutes.

Twenty-two children (6.9%) had underlying disease consisting of allergic disease or thalassemia. Developmental delay was present upon first examination in 10 children (3.1%). Seventy-six (22.9%) had family history of febrile seizure and 3 (0.9%) had epilepsy in first degree relation.

Upon the clinical examination, mean body temperature was 38.8 degrees Celsius (SD 0.85). The median pulse rate was 140 bpm (range 70 to 197 bpm). All patients had normal weight, height and head circumference. Mild or moderate dehydration was presented as 40.1% or 6.6%, respectively. One child (0.3%) had positive meningeal sign. Two (0.6%) children were comatose briefly after febrile status epilepticus.

The most frequent etiology of fever was respiratory tract infection (58%), followed by acute gastroenteritis (15%) and viral exanthem (7%) such as enteroviral infection and roseola infantum (Table 1). Dehydration was found almost half of subjects (46.7%) and showed significantly associated with hyponatremia ($P < 0.05$).

There was a high rate of laboratory investigation in children presenting with first seizure and fever. Electrolytes measurement and complete blood count were done in all 319 (100%). Urinanalysis, serum calcium, serum magnesium, BUN, and creatinine were done in 292 - 300 (91.5 - 94%). Serum phosphate and blood sugar were measured in 223 - 246 (70 - 77.1%).

Detailed laboratory results are shown in Table 2. Lumbar puncture and complete CSF analysis were performed for 142 children (44.5%). Of these, CSF profile was abnormal in 52 children (36.6%). The most common abnormal finding was low glucose ratio (44/142, 31%). The child with positive meningeal sign of WBC 205 /mm^3, and glucose ratio 0.49, was diagnosed with viral meningitis.

Table 2. Laboratory findings of 1st episode seizure with fever.

Laboratory data(N*)	**N (%)**	**Range (Mean ± SD)**
Electrolyte (mmol/L)		
Sodium level (N = 319)		129 -144 (136.1 ± 2.5)
Mild hyponatremia	77 (24.1)	
Moderate hyponatremia	2 (0.6)	
Potassium level (N = 319)		3.3 - 6 (4.3 ± 0.4)
Hypokalemia	0 (0)	
Chloride level (N = 319)		92 - 109 (100.7 ± 2.9)
Hypochloridemia	0 (0)	
Bicarb level (N = 318)		10 - 24 (16.9 ± 2.4)
Metabolic Acidosis	281 (88.1)	
Other electrolytes (mg/dL)		
Calcium level (N = 300)		8.3 - 11.1 (9.7 ± 0.5)
Hypocalcemia	7 (2.3)	
Magnesium level (N = 299)		1.56 - 2.8 (2.3 ± 0.2)
Hypomagnesemia	0 (0)	
Phosphate level (N = 223)		3 - 7.7 (5 ± 0.7)
Hypophosphatemia	0 (0)	
Blood sugar level (N = 246) (mg %)		56 - 222 (116.1 ± 31.9)
Hyperglycemia	7 (2.8)	
BUN/Cr ratio (N = 292)		
more than 20	3 (1)	
CBC (N = 319)		
Anemia for age	80 (25.1)	
Leukocytosis	165 (51.7)	
Band form	146 (45.8)	
Urine analysis (N = 292)		
Urine specific gravity > 1.030	3 (1)	
Urine ketone positive	87 (29.8)	
CSF analysis (N=142)		
WBC >5 cell/mm^3	5 (3.5)	
Glucose ratio < 0.6	45 (31.7)	
Protein > 50 mg/dL	4 (2.8)	
- Positive gram strain or culture	0 (0)	

*N = Number tested

Table 3 compared data of the simple and complex febrile seizure groups. Statistically significant factors related to complex febrile seizure included delayed development and family history of febrile seizure or epilepsy in first degree relatives. Hyponatremia, hypocalcemia, metabolic acidosis, anemia, leukocytosis, band form neutrophils and higher BUN to creatinine ratio had no significantly related to type of febrile seizure.

Discussion

In recent multicenter studies (5 - 13) and the 2011 AAP guidelines, some children with febrile seizure were found to have abnormal serum electrolyte values. However, it was concluded that diagnostic testing is unnecessary in most patients with simple febrile seizures.

In the instant study, 319 children presented with first seizure and fever and almost all were diagnosed with febrile seizure (99.9%). Electrolytes were tested in 223 - 300 children (70 - 94%). Abnormal blood test results included hyponatremia, metabolic acidosis, hypocalcemia, hyperglycemia and high BUN/Cr ratio. However, these abnormal levels were not low enough to cause the seizure. Therefore there is no recommendation to do the electrolyte testing in febrile seizure. Nevertheless, dehydration and mild or moderate hyponatremia were associated. Therefore, in cases of dehydration, serum sodium should be considered to test to correct hyponatremia.

In a previous study, Donaldson D, et al. [6], studied in 60 children from 6 months to 8 years, showed that metabolic acidosis (23%), anemia (10%), leukocytosis (35%) and hypomagnesemia (3%) were found in febrile seizure cases. They recommended that in the first simple febrile seizure, routine hematological and biochemical tests were unnecessary. Similarly, in our studies, we found metabolic acidosis (88.1%), anemia (25.1%) and leukocytosis (51.7%). However, there was no evidence

Table 3. Characteristic data compared between simple and complex febrile seizure.

Characteristics (N*)	**Simple FS N (%)**	**Complex FS N (%)**	***P* - value**
Sex (N = 318) Male (182)	151 (56.8)	31 (58.5)	0.960
Positive family history of seizure (N = 318)	56 (21.1)	20 (37.7)	0.016
Delayed development (N = 318)	5 (1.9)	5 (9.4)	0.014
Hyponatremia (N = 318)	63 (23.8)	16 (30.2)	0.416
Hypocalcemia (N = 299)	6 (2.4)	1 (2)	1
Metabolic acidosis (N = 318)	234 (88.3)	46 (86.8)	0.938
Anemia for age (N = 318)	68 (25.7)	11 (20.8)	0.562
Leukocytosis (N=318)	132 (49.8)	32 (60.4)	0.21
Band form neutrophils (N = 318)	124 (46.8)	21 (39.6)	0.42
Dehydration (N = 318)	124 (46.8)	25 (47.2)	1.00

*N = Number tested

of hypomagnesemia and in our study, there was an evidence of hyponatremia (24.7%), and band form neutrophils (45.8%). Therefore, we concur in the conclusion that the routine hematological and biochemical tests are unnecessary in first FS cases.

A previous study in Thailand, Ariyapasid P, et al. [7], studied in 142 children from 6 months to 5 years, showed results similar to our findings. In that previous study, first seizure with fever was predominantly male (57.7%). The most common cause of fever was URI (57.7%). Abnormal laboratory findings were anemia (22.9%) and metabolic acidosis (84.1%). Whereas, in the present study, first seizure with fever was predominantly male (57.1%) and the most common cause of fever was URI (58%).

According to AAP 2011 recommendations [1], the cause of the child's fever should be identified. In the present study, abnormal results revealed by hematologic testing included anemia for age (25.1%), leukocytosis (51.7%) and band form neutrophils (45.8%). Abnormality revealed by urine analysis included high urine specific gravity (1%) and positive ketone (29.8%). These abnormalities did not cause the seizure. However, CBC and UA should be tested for the purpose of searching for the cause of fever.

The AAP guidelines recommend that the lumbar puncture should be performed if the child is appearing ill or otherwise exhibit clinical signs or symptoms. A lumbar puncture is an option in a child 6 to 12 months of age who lacks *Haemophilus influenza type b (Hib)* or *Streptococcus pneumonia* immunizations or for whom immunization status is unknown. It is also an option in children who have been pretreated with antibiotics. [1] In the present study, these guidelines were exceeded. In our country, *Haemophilus influenza type b (Hib) and Streptococcus pneumonia* vaccine are not on the national schedule. Consequently, lumbar puncture is more routinely use to detect these bacteria. Therefore, lumbar puncture was done in all children under 1 ½ year in the first 3 years of the study. In the last 2 years study, all children under 1 year received lumbar puncture and children between 1 and 1 ½ year received with test depending upon clinical evaluation. In total 142 children (44.5%) had lumbar puncture for CSF analysis. There was only 1 patient who was ultimately diagnosed with viral meningitis. We recommend the children less than 1 year of age who present with first seizure and fever, lumbar puncture should be performed. This is not only detecting bacteria, but also to rule out viral meningitis.

Some several recent publications [8 - 10] suggest that serum sodium levels are lower in children with complexes FS. However, other 3 studies found there was no significant association between serum sodium and complex FS. Our study, collaborate these latter, there was no statistically significant difference in mean of serum sodium between children with simple [136.1 (SD 2.44) mmol/L] and complex [136.2 (SD 2.72) mmol/L] FS.

In a study, Tosawat J, et al. [14], showed delayed development and family history of febrile seizure or epilepsy were the predictive risk factors for complex febrile seizure. This findings collaborated by our study. They were statistically significant association between delayed development and family history of seizure. These findings are very helpful in predicting complex febrile seizure occurring during the febrile illness. Therefore, it is highly recommended to consider to collecting information about family history and assessing the present of the possible the development delay in the patient and family members.

In summary, base on our study, certain recommendations for clinical practice can be made. First, it is recommended routine hematologic or electrolyte testing no longer be done in every case of febrile seizure, however, electrolyte testing should be considered in the child who is dehydrated to correct hyponatremia. Second, hematologic and urine testing should be done for the purpose of looking for the cause of fever. Third, lumbar puncture should be performed in children under 1 year to rule out meningitis. Finally, a complete family history of seizure should be collected and the presence of developmental delay should be assessed in order to help predict the occurring of complex FS.

The limitations of this study are the retrospective chart review and data which depend on the accuracy of medical records. There is no problem with the accuracy of laboratory testing because the results are electronically recorded. However, the accuracy of the medical history depends upon the thoroughness and skill of the personnel taking the history. A further limitation is that the subjects in this study were collected from only one center in Bangkok, and therefore might not represent the children from other areas.

Conclusion

The level of metabolic disturbance was not significantly associated with the febrile seizure. As a result, laboratory investigations are no longer recommended for all patients, except in the presence of clinically suspicious factors, e.g., dehydration, electrolyte loss, dysmorphic features or diseases involving metabolic disturbance.

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Ethical Approval

This review has been approved by the Ethics Committee of Bhumibol Adulyadej Hospital.

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