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Association between Hypocapnea and Febrile Seizures

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ABSTRACT

Background: Although a number of susceptibility genes and environmental factors have been identified, precise mechanism that triggers febrile seizures (FS) is still unclear. However, it is known that pH changes have central role in the control of electrical activity in brain, leading to seizures. Brain alkalosis is known to enhance neuronal excitability and promote epileptiform activity.

Objective: The aim of this study was to assess the association between febrile seizure and hypocapnea and the role of hypocapnea in the development of febrile seizures.

Patients and Methods: The present study was an observational, case-control, study that was conducted on 100 patients who were recruited form Aswan University Hospitals. The patients were divided into the following groups: **Group I:** 50 children with febrile seizure (defined as: seizures in children in association with fever of 38.0 C or more without definitive evidence of neurological disorders, central nervous system infection, or metabolic abnormalities). **Group II:** 50 age- and gender-matched children with febrile illness, but without convulsions working as a control group.

Results: We found that there was statistically significant difference between patients and control groups in terms of hypocapnea ($p < 0.001$). Patients were more likely to have hypocapnea at admission. In addition, there were statistically significant differences between patients and control groups in terms of acidosis at admission ($p < 0.001$) and alkalosis at admission ($p < 0.001$). Patients were more likely to have acidosis or alkalosis.

Conclusion: Hypocapnea is significantly associated with febrile seizures. In our study, we found that children with febrile convulsion had significantly higher rate of hypocapnea than normal controls. In addition, it is apparent that presence of hypocapnea is associated with the type of seizure, but not with the duration of the attack.

Keywords: Hypocapnea, Febrile Seizures, Children.

INTRODUCTION

FS is one of the most common types of seizures in children aged between 5 months and 5 years and accounts for 30% of all childhood seizures [(1)]. the American Academy of Pediatrics (AAP) has announced a standard definition of febrile seizures as a seizure occurring in febrile children between the ages of 6 and 60 months who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizures [(2)]. FS can be separated into two categories, simple and complex. A simple FS is isolated, brief and generalized. Complex FS is one with focal onset, one that occurs more than once during a febrile illness, or one that lasts more than 10 to 15 minutes [(3)]. Simple FS have an age range classically described as 6 to 60 months. The peak incidence is usually in the second year of life. FS are prevalent in up to 5% of children, with the overall incidence estimated to be 460/100,000 in the age group of 0–4 years. Most FS are simple; however, up to 30% might have some complex features [(4)].

Genetic and environmental factors are thought to contribute to febrile epileptogenesis. Although a number of susceptibility genes associated with fever-induced convulsions have been identified, the precise epileptogenic mechanisms have not been determined [(4)].

Fever is an elevation of body temperature induced by the thermoregulatory center of the hypothalamus in response to certain situations. This sign is believed to be an adaptive mechanism, developed with the purpose of stimulating the immune system and preserving cell membrane integrity in the presence of threats. Although there is broad disagreement in the literature concerning normal body temperature in children, normal axillary temperature is generally considered to range between 36.0°C in the morning to 37.7º.C in the afternoon. Any values above this range should be regarded as abnormal [(5)]. pH changes have a central role in the control of seizure activity in the brain. Alkalosis is known to enhance neuronal excitability and to promote epileptiform activity, both in vitro and in vivo. in line with this, hyperventilation (which by definition leads to a net loss of CO_2 and to consequent respiratory alkalosis) is a standard method to provoke absence seizures, complex partial seizures, and other epileptiform manifestations in human patients [(6)].

The pathophysiological link between fever and increased seizures susceptibility had been researched in rats. In mouse modules, hyperthermia cause hyperventilation with intracerebral hypocapnea (alkalosis) and seizures [(7)].

Kilicaslan *et al.* [(8)] measured both blood pH and PCO_2 within 1 hour after the FS and 1 hour of febrile

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period of control group. There was no significant difference in mean blood pH between the FS and control groups, but blood PCO_2 was significantly lower in the FS group. At 24 hours after the FS event, PCO_2 was not significantly different from that measured in the control fever patients. Patients with complex febrile seizures exhibited significantly lower PCO_2 levels within 1 hour of febrile seizure onset than did patients with simplex febrile seizures, whereas there was no significant difference in pH between these 2 groups at either 1 hour or 24 hours after the febrile seizure event.

The aim of this study was to assess the association between febrile seizure and hypocapnea and the role of hypocapnea in the development of febrile seizures. In addition, we aimed to identify whether hypocapnea affects the type of seizure and its duration, and if there is a difference between acidosis and alkalosis on different disease parameters.

PATIENTS AND METHODS

Observational case-control study on 100 patients who were recruited form Aswan University Hospitals. The patients were divided into the following groups:

Group I: 50 children with febrile seizure (defined as: seizures in children in association with fever of 38.0 C or more without definitive evidence of neurological disorders, central nervous system infection, or metabolic abnormalities) admitted to the Pediatric Emergency Department at Aswan university hospital.

Group II: 50 age- and gender-matched children with febrile illness but without convulsions working as a control group.

Inclusion criteria: Patients with febrile convulsions with convulsive seizure associated with fever of 38 C or more. Age ranged from 6 to 60 months. Both sexes were included.

Exclusion criteria: Children with definitive evidence of neurological illness, central nervous system (CNS) infection, metabolic abnormalities or poisoning. Children had gastroenteritis or lower respiratory tract infection to exclude the possibility of acidosis. Patients aged more than 5 years and less than 6 months. Patients with positive family history of convulsion.

Sample Size and Sampling: We utilized non-probability consecutive sampling technique. A total of 100 children were determined to be included in the present study.

Data Collection:

All included patients were interviewed and data were collected in the form of structured questionnaire (was filled from parents or caregivers of the included children), which includes the following data:

1. **Full history taking**: Child sex, age and residency. For patients with febrile seizures: duration of febrile seizures, history of previous febrile seizures, family history of febrile seizures, and the type of seizures (simple febrile seizure or complex febrile seizure) were recorded.
2. **Full physical examination,** some anthropometric measurements (weight & height).
3. **Laboratory investigations include:** Complete blood count (CBC). Venous blood gases upon admission and after 24 hours. C - reactive protein (CRP).
4.

Complete blood picture (CBC) methodology:

Sample: 2 ml of venous blood has been drawn from each case on EDTA tube for complete blood picture.

Sample processing: Complete blood picture has been done on automated cell counter (Sysmex-XP 300) with complete red blood cell indices assessment (MCV, MCH and MCHC).

Venous Blood Gases Methodology:

Sample: Samples were drawn from brachial vein in heparinized insulin syringe as soon as a child presented to emergency, taking all aseptic precautions, and immediately transferred to laboratory on iceboxes. The syringes were pre-heparinized and handled to minimize air exposure that will alter the blood gas values.

Sample processing: Automated blood gas analyzer (GEM Premier 3500, Instrumentation Laboratory, Bedford, Massachusetts, USA) was used to analyze blood gas samples, and results were obtained within 10-15 minutes.

Normal values: Results were compared with standard values: pH, 7.35–7.45; pCO2, 35–45mm Hg; and base excess –2 to +2.

CRP Methodology:

Fasting samples were collected for CRP level measurement (time of the blood sample from last seizure > 6 h and > 48 h from status epilepticus, as they are sampled from stable patients at their follow up in the outpatient clinic). Blood samples (3 mL) were withdrawn from peripheral veins, left at room temperature for 30 min then centrifuged at 3000 r/min for 10 min to separate the sera, to analyze levels of CRP by enzyme-linked immunosorbent assay (ELISA). Sera were stored at −20°C till the time of assay. CRP concentration was determined using commercially available kits [Immunospec Corporation (sunred) Co., China]. The principal of the assay for CRP was ELISA for the detection and quantification of biological molecules secreted or released by cells. This method immobilizes and binds a target-specific captured antibody onto a high protein by ELISA plate, which in turn enables the capture of target protein. The captured protein is then detected by a protein-specific biotinylated antibody using Stat Fax 2100 microplate reader.

Study's Outcomes:

The primary outcome in the present study was to assess the association between febrile seizure and hypocapnea and the role of hypocapnea in the development of febrile seizures. The secondary outcome was to identify whether hypocapnea affects the type of seizure and its duration.

Ethical Statement:

We confirm that the present study run in concordance with International Ethical Standards and applicable local regulatory guidelines. A written informed consent was obtained from the parents of every eligible patient. Parents were informed about the study objectives, methodology, risk, and benefit. **The study's protocol was reviewed and approved by Institutional Review Board (IRB) Ethics Committee or Audit Department of Faculty of Medicine, Aswan University.**

Statistical Analysis

An Excel spreadsheet was established for the entry of data. We used validation checks on numerical variables and option-based data entry method for categorical variables to reduce potential errors. The analyses were carried with SPSS software (Statistical Package for the Social Sciences, version 24, SSPS Inc, Chicago, IL, USA). The normality of the data were assessed using Shapiro-Wilk test. Numerical data were described as mean ± SD if normally distributed; or median and interquartile range [IQR] if not normally distributed. Frequency tables with percentages were used for categorical variables. Independent Student t-test and paired t-test were used to compare parametric quantitative variables, while Mann-Whitney tests and Wilcoxon matched pairs test were used to compare non-parametric quantitative variables. Chi-square test or McNemar-Bowker test were used to analyze categorical variables. Multilinear logistic regression was undertaken to assess the predictors of mortality. A p-value ≤ 0.05 is considered statistically significant.

RESULTS

The mean age of the included patients in group I was 2.16 ± 0.85 years compared to 2.12 ± 0.82 in the control group (p =0.77). The majority of the patients were males in both groups (68% versus 56%, p = 0.54). None of the patients had family history of seizure.

Table (1): The demographic characteristics of the included patients.

Variables	Patients (N =50)	Control (N =50)	P-value
Age in years Mean ± SD	2.16 ± 0.85	2.12 ± 0.82	0.77
Median (range)	2 (1 -4)	2 (1 -4)	
Gender, No. (%)			
Male	32 (68%)	28 (56%)	0.54
Female	18 (36%)	22 (44%)	
Family History, No. (%)			
Yes	22 (31.4%)	0	NA
No	28 (68.6%)	50	

*Data are presented as mean ±SD, median (Range), or number (%).

Table (2): Relation between pH findings and febrile seizure.

Variables	Patients (N =50)	Control (N =50)	P – value
Acidosis at admission, No. (%)			
Yes	7 (14%)	1 (2%)	<0.001
No	43 (86%)	49 (98%)	
Alkalosis at admission, No. (%)			
Yes	19 (38%)	0	<0.001
No	31 (62%)	50 (100%)	
Normal pH, No. (%)			
Yes	24 (48%)	49 (98%)	<0.001
No	26 (52%)	1 (2%)	

*Data are presented as mean ± SD or number (%).

Table (2) showed the relation between pH findings and febrile seizure. There were statistically significant differences between patients and control group in terms of acidosis at admission ($p < 0.001$) and alkalosis at admission ($p < 0.001$).

Patients were more likely to have acidosis or alkalosis.

Table (3): Relation between hypocapnea and febrile seizure.

Variables	Patients (N =50)	Control (N =50)	P – value
Hypocapnea, No. (%)			
Yes	37 (74%)	6 (12%)	<0.001

No	13 (26%)	42 (88%)	

*Data are presented as mean ±SD or number (%).

Table (3) showed the relation between hypocapnea and febrile seizure. There was statistically significant difference between patients and control group in terms of hypocapnea (p <0.001). Patients were more likely to have hypocapnea at admission.

Table (4): The relation between disease characteristics and presence of hypocapnea.

Variables	Hypocapnea (N =37)	Normal pCO2 (N =13)	P-value
Type of Seizure, No. (%)			
Tonic Tonic-Clonic	4 (10.8%) 33 (89.2%)	0 13 (100%)	<0.001
Duration of attack in minute			
Mean ± SD Median (range)	3.2 ± 0.85 3 (2 -5)	3.6 ± 0.86 3 (2 -5)	0.168

*Data are presented as mean ±SD, median (Range), or number (%).

Table (4) showed the relation between disease characteristics and presence of hypocapnea. There was statistically significant association between type of seizure and the presence of hypocapnea (p < 0.001). On the other hand, there was no statistically significant association between duration of attack and the presence of hypocapnea (p < 0.168).

Table (5): The relation between abnormal ABG findings and demographic characteristics of the included patients**.**

Variables	Acidosis and hypocapnea (N =7)	Alkalosis and hypocapnea (N =19)	P-value
Age in years			
Mean ± SD	1.43 ± 0.44	2.17 ± 0.78	0.041
Gender, No. (%)			
Male Female	5 (71.4%) 2 (28.6%)	5 (26.3%) 14 (73.6%)	0.001

*Data are presented as mean ±SD, median (Range), or number (%).

Table (5) showed the relation between abnormal ABG findings and demographic characteristics of the included patients. There were statistically significant associations between the ABG findings and age (p =0.041) and gender (p =0.001).

Table (6): The relation between abnormal ABG findings and disease characteristics of the included patients.

Variables	Acidosis and hypo-capnea (N =7)	Alkalosis and hypo-capnea (N =19)	P-value
Age at onset in years Mean ± SD	1.42 ± 0.44	2.2 ± 0.87	0.041
Type of Seizure, No. (%) Tonic Tonic-Clonic	0 7 (100%)	0 19 (100%)	NA
Duration of attack in minutes Mean ± SD	2.7 ± 0.48	3.73 ± 0.93	0.01
Temperature in C Mean ± SD	39.4 ± 0.38	38.62 ± 0.61	0.002
Type of Infection, No. (%) OM Tonsillitis UTI	5 (71.4%) 2 (28.6%) 0	11 (57.9%) 5 (26.3%) 3 (15.8%)	0.73

*Data are presented as mean ±SD, median (Range), or number (%).

Table (6) showed the relation between abnormal ABG findings and disease characteristics of the included patients.

There were statistically significant associations between ABG findings and age at onset (p = 0.04), duration of attack (p = 0.011, and temperature (p = 0.002). In contrary, there were no statistically significant associations between ABG findings and type of seizure and type of infection (p =0.73).

Table (7): The relation between abnormal ABG findings and laboratory findings of the included patients.

Variables	Acidosis and hypocapnea (N =7)	Alkalosis and hypocapnea (N =19)	P-value
Hemoglobin (g/dL)	10.5 ± 1.6	9.6 ± 1.2	0.14

MCV (fl)	79.5 ± 7.7	75.7 ± 7.7	0.22
MCHC (g/dL)	32.3 ± 1.7	30.6 ± 1.7	0.1
Platelet ($\times 10^3$/dL)	287.8 ± 19.1	474.8 ± 72.1	0.33
WBC ($\times 10^3$/dL)	11.2 ± 2.1	10.3 ± 2.1	0.61
Neutrophil Count	6.3 ± 1.1	6.3 ± 1.1	0.34
Lymphocyte Count	2.3 ± 0.4	2.3 ± 0.4	0.22
CRP (mg/dL)	16.6 ± 4.1	17.6 ± 4.1	0.92

*Data are presented as mean ±SD, median (Range), or number (%).

Table (7) showed the relation between abnormal ABG findings and laboratory findings of the included patients. There were no statistically significant associations between ABG findings with hypocapnea and hemoglobin level (p =0.14), MCV (p =0.22), MCHC (p =0.1), platelet count (p =0.33), WBCs (p =0.61), and CRP (p =0.92).

Table (8): Correlation between different parameters and P CO_2.

	P CO_2 at admission	
	Correlation Coefficient	**P- Value**
Age in years	0.062	0.53
Duration of attack	0.073	0.61
Temperature	-0.08	0.58

*Data are presented as correlation coefficient

Table (8) showed correlation between different parameters and PCO_2.

DISCUSSION

In the present study, we found that mean age of the included patients in group I was 2.16 ± 0.85 years and 2.12 ± 0.82 in the control group. The majority of the patients were males in both groups (68% and 56% in G I and II respectively). In line with these findings, **Hussain *et al.*** [9] conducted a hospital-based prospective study on 100 children with febrile convulsion, they concluded that 68% were males and 32% were females. Mean age of their pateints was 22.58 ± 12.50 months. In addition, **Potdar** [10] aimed to study the demographic profile and some risk factors of febrile seizures among children. Of 288 children with febrile convulsion, 60.1% were boys and the mean age of occurrence was 2.8 years ± 1.5 years. Febrile seizures usually occur in children between 6 months and 5 years of age. In addition, a mild male predominance was reported for febrile seizure incidence [4].

Regarding the disease characteristics in our study, we found that the type of seizure was tonic-clonic in the majority of the cases (92%) and the mean duration of attack was 3.32 ± 0.86 minutes. Similar to our findings, **Shrestha *et al.*** [11] evaluated the clinical profile of children presenting with febrile seizure. This was a descriptive retrospective study among children presenting with febrile seizure in a teaching hospital from July 2009 to June 2013. This study included 103 children with febrile seizure. Simple febrile seizure and complex febrile seizure were observed in 76.7% and 23.3% of patients respectively. Majority of children (71.8%) had generalized tonic clonic seizure followed by tonic seizures. Moreover, **Bassan *et al.*** [12] obtained data, prospectively, on all children who presented from January 2008 to March 2010 with febrile seizure to the emergency rooms of four medical centers. Sixty children were included. Majority of children (71.8%) had generalized tonic clonic seizure followed by tonic seizures. Likewise, **Mwipopo *et al.*** [13] study aimed to determine profile, clinical spectrum and analyze the commonest etiology of seizures in children admitted to a tertiary hospital in Central China. This was a hospital-based retrospective study carried out in Zhongnan Hospital of Wuhan University, China. A total of 200 patients were admitted with seizures. Generalized tonic-clonic seizure was the most common seizure type in 98% of children.

Viral infection is the cause of fever in approximately 80% of cases of febrile seizures. Viral upper respiratory tract infection, pharyngitis, otitis media, and Shigella gastroenteritis are other important causes of febrile seizure [9].

In the present study, 60% of the patients had otitis media, 24% had tonsillitis, and 16% had urinary tract infection. In line with our findings, **Kantamalee *et al.*** [14] aimed to describe clinical characteristics of children with febrile seizures and to identify risk factors for developing recurrent seizures. A retrospective study was conducted from January 2004 to December 2013 in Chiang Mai University Hospital. Respiratory tract infections and otitis media were the most frequent etiology of febrile illnesses. Similarly, **Winkler *et al.*** [15] conducted a hospital-based study on clinical characteristics of children with febrile seizures. Over 2 years, the incidence of febrile seizures was 4% of all admitted children aged < 10 years, with a mortality of almost 4%. On examination, which in most cases was performed on the next day, diagnoses mainly pertained to the respiratory and gastrointestinal tract

Febrile seizures and high fever are characteristic for the high dynamic of infection development. Infection symptoms are associated with an increase in inflammatory factors. The peak of inflammatory markers such as CRP, procalcitonin, leukocytosis is slower than the clinical symptoms [16]. Our analysis showed that children with febrile seizures had statistically significant higher levels of total leucocytic count (TLC), C-reactive protein (CRP), and platelet count. In agreement with our findings, **Gontko–Romanowska *et al.*** [17] assessed selected laboratory results in children with fever without seizures and febrile seizure. The paper presents an analysis of a group of 306 children aged 6 months – 5 years who were admitted with diagnosed fever without seizures and febrile seizures in Specialized Health Care Centre for Mother and Child in Poznan between 1st January 2008 and 31st December 2009. Children with febrile seizures had statistically significant higher levels of TLC, CRP and platelet count

In terms of the primary outcome of the present study, we found that there was statistically significant difference between patients and control groups in terms of hypocapnea ($p < 0.001$). Patients were more likely to have hypocapnea at admission. In addition, there were statistically significant differences between patients and control groups in terms of acidosis at admission ($p < 0.001$) and alkalosis at admission ($p < 0.001$). Patients were more likely to have acidosis or alkalosis. In concordance with our findings, **Marzouk** [7] aimed to evaluate the venous blood gas status in children with febrile seizures and to determine whether hypocapnea is secondary to hyperthermia, induced hyperventilation was associated with febrile seizures in children. The study enrolled 43 individuals, twenty-two children with febrile seizures, together with 21 controls (children with febrile illness without seizures). There were significant differences in mean blood pH and PCO_2 between the febrile seizure and control groups ($p < 0.001$).

This significant association between hypocapnia and febrile convulsion can be explained by previous animal studies, which showed that any changes in blood pH and PCO_2 levels increase or decrease neuronal excitability. These studies concluded that fall in PCO_2 increases neuronal excitability of postsynaptic cells without altering neurotransmitter release in anesthetized rats. It was further shown that hypocapnea increases spike trigger in hippocampus in both the in situ and in vitro population. **Schuchmann *et al.*** [18] using an animal model of experimental febrile seizure, showed that hyperthermia caused respiratory alkalosis with consequent brain alkalosis and seizures.

Seizures and epilepsy have been observed in children with systemic alkalosis of various origins. **Takahashi *et al.*** [19] showed activation procedures such as hyperventilation that induces epileptiform discharges in EEG among susceptible children. In contrast to this, a fall in brain pH is known to suppress neuronal excitability and epileptiform activity. It is important to note that the overall effect on acid–base equilibrium depends on the change in respiratory rate that controls the net flux of CO_2 and on the kidneys that control the excretion of bicarbonates.

Regarding the association between hypocapnea and seizure's characteristics, there was statistically significant association between type of seizure and the presence of hypocapnea ($p < 0.001$). On the other hand, there was no statistically significant association between duration of attack and the presence of hypocapnea ($p < 0.168$).

However, the published literature showed conflicting results regarding the association between hypocapnia and seizure's characteristics. For example **Marzouk** [7] found no significant difference in pH values between the children with complex febrile seizure and those with simple febrile seizure. However, children with complex febrile seizure had significantly lower PCO_2 within 1 h of seizure attack than those with simple febrile seizure. In addition, there was a significant correlation between duration of the seizure attack and PCO_2 value within 1 h of seizure.

While **Kilicaslan *et al.*** [8] showed that patients with complex febrile seizures exhibited significantly lower PCO_2 levels within 1 hour of seizure onset than patients with simple febrile seizures. The difference between our findings and the abovementioned studies could be explained by the difference in population's characteristics. It was reported that the characteristics of febrile seizure varies significantly by geographical region.

CONCLUSION

In conclusion, hypocapnea is significantly associated with febrile seizures. In our study, we found that children with febrile convulsion had significantly higher rate of hypocapnea than normal controls. In addition, it is apparent that presence of hypocapnia is associated with type of seizure, but not the duration of the attack. These findings are very important as it confirms that hypocapnea may be one of the main mechanisms for the initiation and maintenance of seizures. Thus, it is important to study this possible association between febrile seizures and hypocapnea in a larger number of children with febrile convulsions. In addition, the possible use of carbon dioxide for the treatment of febrile seizure may be required to be studied in multicenter researches involving large sample size.

RECOMMENDATIONS

The possible use of carbon dioxide for the treatment of febrile seizure may be required to be studied in multicenter researches involving large sample size.

REFERENCES

1. **Ohlraun S, Wollersheim T, Weib C *et al.* (2013):** Carbon dioxide for the treatment of febrile seizures: rationale, feasibility, and design of CARDIFstudy. J Transl Med., 11: 157-161.
2. **Leung A, Hon K, Leung T (2018):** Febrile seizures: An overview. Drugs Context, 7: 212536-39.
3. **Syndi Seinfeld D, Pellock J (2013):** Recent Research on Febrile Seizures: A Review. J Neurol Neurophysiol., 4 (165): 19519.
4. **Khair A, E lmagrabi D (2015):** Febrile Seizures and Febrile Seizure Syndromes: An Updated Overview of Old and Current Knowledge. https://www.hindawi.Com /journals/ nri/2015/849341/
5. **de Siqueira L (2010):** febrile seizures: update on diagnosis and management. Rev Assoc Med Bras., 56 (4): 489-92.
6. **Schuchmann S, Hauck S, Henning S *et al.* (2011):** Respiratory alkalosis in children with febrile seizures. Epilepsia , 52 (11): 1949–1955.
7. **Marzouk H (2015):** Relevance of hypocapnia to febrile seizures in children. Egypt Pediatr Assoc Gaz., 63: 98–102.
8. **Kilicaslan B, Erol I, Ozkale Y *et al.* (2014):** Association between hypocapnia and febrile seizures. J Child Neurol., 29: 599–602.
9. **Hussain S, Tarar S, Sabir M (2015):** Febrile seizrues: Demographic, clinical and etiological profile of children admitted with febrile seizures in a tertiary care hospital. J Pak Med Assoc., 65: 1008–10.
10. **Potdar P (2018):** A retrospective study of febrile seizures among children admitted in a tertiary care hospital. Int J Community Med Public Heal, 5: 3121-24.
11. **Shrestha D, Dhakal A, Shakya H *et al.* (2014):** Clinical characteristics of children with febrile seizure 2014. J Nepal Health Res Counc., 12: 162–6.
12. **Bassan H, Barzilay M, Shinnar S *et al.* (2013):** Prolonged febrile seizures, clinical characteristics, and acute management. Epilepsia , 54: 1092–8.
13. **Mwipopo E, Akhatar S, Fan P *et al.* (2016):** Profile and clinical characterization of seizures in hospitalized children. Pan Afr Med J., 24: 313-317.
14. **Kantamalee W, Katanyuwong K, Louthrenoo O (2017):** Clinical characteristics of febrile seizures and risk factors of its recurrence in chiang mai university hospital. Neurol Asia., 22: 203–8.
15. **Winkler A, Tluway A, Schmutzhard E (2013):** Febrile Seizures in Rural Tanzania: Hospital-based Incidence and Clinical Characteristics. J Trop Pediatr., 59: 298–304.
16. **Sohn H, Kim S, Lee S (2016)** Inflammatory markers associated with seizures. Epileptic Disord., 18: 51–7.
17. **Gontko-Romanowska K, Żaba Z, Panieński P *et al.* (2017):** The assessment of risk factors for febrile seizures in children. Neurol Neurochir Pol., 51: 454–8.
18. **Schuchmann S, Hauck S, Henning S *et al.* (2011):** Respiratory alkalosis in children with febrile seizures. Epilepsia , 52: 1949–55.
19. **Takahashi T, Chiappa K (2012):** Activation methods. Niedermeyer's Electroencephalogr. Basic Princ. Clin. Appl. Relat. Fields Sixth Ed., Pp:215–38.