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Relevance of hypocapnia to febrile seizures in children

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Abstract *Background:* Febrile seizure is the most common type of convulsion in children. However, there are scanty data on the mechanism of its development. The aim of this study was to evaluate the venous blood gas status in children with febrile seizures and to determine whether hypocapnia secondary to hyperthermia-induced hyperventilation was associated with febrile seizures in children.

Patients and methods: The study enrolled 43 individuals, twenty-two children with febrile seizures, together with 21 controls (children with febrile illness without seizures). Venous blood gases were determined in the febrile seizure group within 1 h and at 24 h after a seizure attack while, venous blood gases were measured once in the control group within 1 h after a febrile period.

Results: There were significant differences in mean blood pH and P_{CO_2} between the febrile seizure and control groups ($p < 0.001$). There was 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 P_{CO_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 P_{CO_2} value within 1 h of seizure.

Conclusion: The results of the present study confirmed the association between febrile seizure and hypocapnia and that supported the role of hypocapnia in the development of febrile seizures.

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Introduction

Febrile seizure is one of the most common types of seizure in children aged between 5 months and 5 years and accounts for 30% of all childhood seizures.^{1,2} This convulsion is considered as the response of immature brain of children to fever,

without any intracranial infection or other defined cause.³ Peak incidence of febrile seizures is at the age of 16–18 months.^{4–8}

Most febrile seizures have a good prognosis. However, children with a simple febrile seizure have a risk of recurrence and an increased risk to develop epilepsy in 2.4–8.0% of affected children by adolescence.^{9–13}

Simple febrile seizures mainly occur within the first 24 h of a febrile illness, last less than 15 min, only once during a febrile illness and don't show a focal pattern. In contrast, complex

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febrile seizures last longer than 15 min, occur more than once in one febrile episode and may have focal features.^{11,13}

The pathophysiological link between fever and increased seizure susceptibility had been researched in rats. In the mouse models, hyperthermia causes hyperventilation with intracerebral hypocapnia (alkalosis) and seizures.^{14–16}

Hyperventilation with subsequent respiratory alkalosis is known to induce epileptiform manifestations especially complex partial seizures and absence.¹⁷

In this study, we measured P_{CO_2} and pH values in children with febrile seizures to know whether hyperthermia with subsequent respiratory alkalosis was relevant to febrile seizures in children. This was the second study to compare between children with febrile seizures and those with febrile episodes but without seizures excluding the possibility of acidosis such as respiratory tract infection and gastroenteritis and this study could help in understanding the possible mechanism of febrile seizures in children.

Materials and methods

The study enrolled 43 children including, 22 children with a 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 of the Cairo University Specialized Pediatric Hospital during the period from June 2013 to October 2014. Twenty-one age- and gender-matched children with febrile illness, but without convulsions, were assigned to the control group.

Inclusion criteria for patients with febrile convulsions: age ranged from 6 to 60 months, with convulsive seizure associated with fever of 38 °C or more. Children with definitive evidence of neurological illness, central nervous system (CNS) infection, metabolic abnormalities or poisoning were excluded from the study. Also none of the study populations (patients and controls) had gastroenteritis or lower respiratory tract infection to exclude the possibility of acidosis.

The study was approved by the ethics committee of Faculty of Medicine, Cairo University, and written informed consents were obtained from the parents of all participants.

For all participants, the cause of fever was determined by detailed history and complete physical examination.

For patients with febrile seizures, duration of febrile seizures, history of previous febrile seizures, family history of febrile seizure, and the type of seizures (simple febrile seizure or complex febrile seizure) were recorded.

Venous blood gases were measured in children with febrile seizures within 1 h and at 24 h after seizure attack, while they were measured only once in the control group within 1 h after a febrile period.

Normal values in pediatric age group for pH were defined from 7.35 to 7.45 and for P_{CO_2} 35–45 mmHg.

Statistical analysis

Pre-coded data were entered into the Statistical Package of Social Science Software program, version 21 (SPSS) to be statistically analyzed. Data were summarized using mean, standard deviation for quantitative variables and frequency and percentage for qualitative ones. Comparison between groups was performed using Mann Whitney and Kruskal Wallis tests for quantitative variables and Chi square or Fisher's exact test for qualitative ones. Spearman correlation coefficients were calculated to explore the association between different quantitative variable. p values less than 0.05 were considered statistically significant, and less than 0.01 were considered highly significant.

Graphs were used to illustrate some information.

Results

The study included 22 children with febrile seizures, 12 females and 10 males. Their mean age was 19.3 ± 11.7 months. 40.9% of our cases had family history of febrile seizures and 72.7% of the cases had past history of febrile seizures.

The control group included 21 children with febrile illness but without seizures, 11 females and 10 males. Their mean age was 20.3 ± 13.1 months.

The children in the febrile seizure group were diagnosed with tonsillitis (45.5%), otitis media (22.7%), urinary tract infection (18.2%) and pharyngitis (13.6%). Also, children in the control group were diagnosed with tonsillitis, pharyngitis, urinary tract infection and otitis media (47.6%, 28.6%, 19% and 4.8%, respectively), with no statistically significant difference between both groups.

There was no significant difference between the cases and control groups as regards mean temperature (39.1 ± 0.6, 38.9 ± 0.6, respectively), $p = 0.3$.

Sixteen children were diagnosed with simple seizure (72.7%) and 6 with complex febrile seizures (27.3%).

There were highly significant differences in mean blood pH and P_{CO_2} between the febrile seizure and control groups within 1 h after seizure ($p < 0.001$). At 24 h after seizure attack, there was a highly significant difference in mean blood pH while there was no significant difference in P_{CO_2} between the febrile

Table 1 Comparison between children with febrile seizure and control group as regards blood pH and P_{CO_2} values.

	Children with febrile seizure		Control group		p -Value ^d
	1 h ^a		24 h ^b	1 h ^c	
pH ^e	7.47 ± 0.06		7.42 ± 0.04	7.37 ± 0.03	< 0.001 ^{a,c&b,c}
P_{CO_2} ^e	29.89 ± 2.98		36.01 ± 3.41	37.98 ± 3.90	< 0.001 ^{a,c} and 0.093 ^{b,c}

^a Values in patients with febrile seizures at 1 h.

^b Values in patients with febrile seizures at 24 h.

^c Values in control at 1 h.

^d Significant p -value < 0.05, and highly significant p -value < 0.01.

^e Values are mean ± standard deviation.

Table 2 Comparison of blood pH and P_{CO_2} values in children with febrile seizure as regards gender, past history and family history of febrile seizures.

Blood gases values ^a	Variables		p -Value ^b
	Males ($n = 10$)	Females ($n = 12$)	
pH at 1st h	7.46 ± 0.06	7.47 ± 0.06	0.8
pH at 24 h	7.42 ± 0.04	7.42 ± 0.03	0.9
P_{CO_2} at 1st h	29.35 ± 3.25	30.34 ± 2.79	0.4
P_{CO_2} at 24 h	35.00 ± 2.87	36.86 ± 3.71	0.2
	Children with past history of febrile seizure ($n = 16$)	Children without past history of febrile seizure ($n = 6$)	
pH at 1st h	7.47 ± 0.05	7.46 ± 0.08	0.6
pH at 24 h	7.43 ± 0.04	7.41 ± 0.03	0.5
P_{CO_2} at 1st h	29.83 ± 3.00	30.05 ± 3.19	1.0
P_{CO_2} at 24 h	35.42 ± 3.35	37.60 ± 3.31	0.2
	Children with family history of febrile convulsion ($n = 9$)	Children without family history of febrile convulsion ($n = 13$)	
pH at 1st h	7.49 ± 0.05	7.45 ± 0.06	0.1
pH at 24 h	7.43 ± 0.03	7.41 ± 0.04	0.4
P_{CO_2} at 1 st h	30.01 ± 3.48	29.81 ± 2.73	0.8
P_{CO_2} at 24 h	36.27 ± 3.41	35.84 ± 3.54	0.8

^a Values are mean ± standard deviation.
^b Significant p -value < 0.05, and highly significant p -value < 0.01.

seizure and control groups ($p < 0.001$ and 0.093, respectively) (Table 1).

Within 1 h after the episode, the mean base excess in the febrile seizure and control groups was -4.19 ± 2.12 and -2.28 ± 1.76 , respectively with a significant difference ($p = 0.003$) and was significantly negatively correlated with the duration of seizure attack in the febrile seizure group ($r = -0.5$, $p = 0.018$).

By comparing between the children with a past history of febrile seizures and those without a past history of febrile seizures, mean values of blood P_{CO_2} within 1 h and at 24 h after febrile seizure attack were lower in the children with a past history of febrile seizure with no significant difference ($p = 1.0$ and 0.2, respectively) and no statistically significant difference between both groups as regards mean pH values at either 1 h or 24 h after seizure attack ($p = 0.6$ and 0.5, respectively) (Table 2).

In addition, there was no significant difference between the febrile seizure group with family history of febrile seizure and those with no family history as regards pH and P_{CO_2} values

Table 3 Association between family history and past history of febrile seizure in children with febrile seizures ($n = 22$).

	Family history of febrile seizure				p -Value ^a
	Positive ($n = 9$)		Negative ($n = 13$)		
	N	%	N	%	
Past history of febrile seizure					
Positive ($n = 16$)	8	88.9	8	61.5	0.3
Negative ($n = 6$)	1	11.1	5	38.5	

^a Significant p -value < 0.05, and highly significant p -value < 0.01.

Table 4 Comparison between blood pH and P_{CO_2} values in children with febrile seizure according to the seizure types.

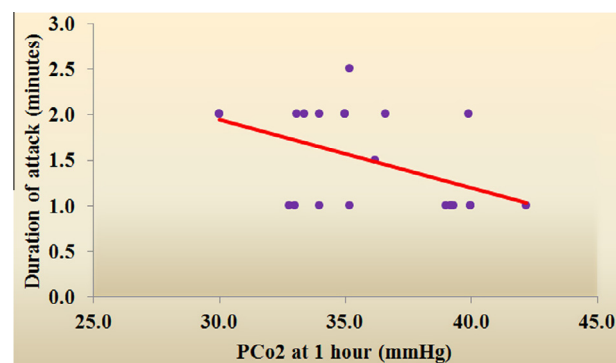
	Simple febrile seizure ($n = 16$)	Complex febrile seizure ($n = 6$)	p -Value ^a
At 1 h ^b			
pH ^c	7.46 ± 0.05	7.49 ± 0.07	0.3
P_{CO_2} ^c	30.68 ± 2.69	27.78 ± 2.88	0.04
At 24 h ^d			
pH ^c	7.42 ± 0.04	7.42 ± 0.03	0.9
P_{CO_2} ^c	36.66 ± 3.27	34.30 ± 3.45	0.1

^a Significant p -value < 0.05, and highly significant p -value < 0.01.

^b Values in patients with febrile seizures at 1 h.

^c Values are mean ± standard deviation.

^d Values in patients with febrile seizures at 24 h.

**Figure 1** Correlation between the duration of febrile seizure attack and P_{CO_2} values at 1 h after seizure ($p = 0.001$).

whether at 1 hr or 24 h after seizures ($p = 0.1$, 0.8 and 0.4, 0.8 respectively) and also there were no significant differences in pH and P_{CO_2} values regarding gender (Table 2). Furthermore, there was no significant association between past history of febrile seizure and family history of febrile seizure ($p = 0.3$) (Table 3).

Children with complex febrile seizure had significantly lower P_{CO_2} within 1 h of febrile seizure than in children with simple febrile seizure ($p = 0.04$), and still lower in children with complex febrile seizure at 24 h after seizure attack but with no significant difference ($p = 0.1$). There was no significant difference in pH values between the two groups either at 1 h or at 24 h after the febrile seizure attack ($p = 0.3$, 0.9, respectively) (Table 4).

There was a significant correlation between the duration of febrile seizure and P_{CO_2} values within 1 h after seizure attack ($r = -0.533, p = 0.01$) (Fig. 1). However, there was no significant correlation between mean temperature and P_{CO_2} values within 1 h after seizure ($p = 0.9$).

Discussion

The aim of this study was to examine blood gas status in Egyptian children with febrile seizure and the potential relationships between hypocapnia and febrile seizure. In children with acute infection, fever is a cause of tachypnea and for every 1° increase in body temperature, there is a 3.7 breath per minute increase. Thus, respiratory rate is partially dependent on body temperature in children with febrile illness.¹⁸ The pathogenesis of febrile seizure is still debated in humans; some studies documented that the genetic factors, immunological disorders, familial background, iron deficiency and zinc deficiency may have a role in febrile seizures.¹⁹ Also, a previous study in young rat revealed that hyperthermia led to thermal tachypnea and respiratory alkalosis that induced and sustained seizures.¹⁶ In addition, two previous studies had investigated the relationship between hypocapnia and febrile seizure, one of those studies compared between febrile children with gastroenteritis and children with febrile seizure.²⁰ In the current study we excluded patients with gastroenteritis and lower respiratory tract infection to rule out the possibility of acidosis as in the study by Kilicaslan et al.¹⁷

The present study detected a significantly higher mean blood pH values in the febrile seizure group ($p < 0.001$), which is consistent with the result of Schuchman et al.²⁰ This was in accordance with what was reported recently by Kilicaslan et al.¹⁷ who similarly conducted their study on a small sample of patients (patients and control). However, despite similar higher mean blood pH values in the febrile seizure group, there was no significant difference in that study.

Also, the current study revealed a significant hypocapnia in febrile seizure group, similar to that reported by Kilicaslan et al.¹⁷ and Schuchman et al.²⁰; this may point to the presence of association between hypocapnia and febrile seizure.

In addition, the present study demonstrated a significant negative correlation between P_{CO_2} values and the duration of seizure ($r = -0.533, p = 0.011$), which is consistent with the results of Morimoto et al.²¹

When stratified according to the type of seizure, the P_{CO_2} values following complex febrile seizures were significantly lower than those measured in children with simple febrile seizures within 1 h after the attack ($p = 0.04$) and that significant difference was not present at 24 h after febrile seizure ($p = 0.9$), that may be more evident if the sample size was larger, this was similar to that reported by Kilicaslan et al.¹⁷

Complex febrile seizure is one of the predisposing factors for the occurrence of epilepsy.²² Thus recurrent hypocapnia may be a possible mechanism for the development of epilepsy.

In the current study, comparing between children with past history of febrile seizure and those with no history of previous febrile seizures revealed no significant difference in P_{CO_2} values. Furthermore, there was no significant association between past history and family history of febrile seizure ($p = 0.3$). However, Sfaihi et al.²³ reported that positive family history of febrile seizure is predictive of recurrent febrile seizure, but

the number of febrile seizure attacks cannot predict the possibility of epilepsy.

Our study did not find any significant difference in pH and P_{CO_2} values between children with positive family history of febrile seizure and those children without family history, which is consistent with the results of Kilicaslan et al.¹⁷

The present study revealed that P_{CO_2} values within 1 h after seizure attack were not significantly correlated with the temperature at the time of admission. This may confirm the role of hypocapnia in the pathogenesis of febrile seizures, which is not dependent on the mean temperature at admission.

To our knowledge, minority of the studies were carried out on this subject. This draws concern for the necessity to investigate the blood gases status in children with febrile seizure on a larger scale for better understanding of the pathogenesis of the disease which by far will affect the management and prognosis.

Conclusion

Our study suggested that hypocapnia associated with febrile seizures may be one of the main mechanisms for the initiation and maintenance of seizures. Also, the complex febrile seizure, which is one of the risk factors of epilepsy, was associated with significant reduction in P_{CO_2} . We believed that the next step is to study this possible association between febrile seizures and hypocapnia 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.

Conflict of interest

None declared.

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