Association of Hypocapnia in Children with Febrile Seizures

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Introduction: Febrile seizure is a benign condition in children. Susceptibility genes associated with febrile convulsions have been identified, but the precise pathophysiologic mechanism that triggers febrile seizure is unclear. Using animal models, it has been demonstrated that hyperthermia causes respiratory alkalosis with consequent brain alkalosis and seizures. This study was conducted to find out any association of febrile seizures with fever induced hypocapnia. Methods: We conducted a cross sectional observational study and enrolled 45 children presenting with febrile seizures. Axillary temperature was measured and venous blood gas analysis was done soon after admission and within 24 hour of seizure onset. Mean pH and pCO2 from venous blood gas analysis was measured and compared with standard normal values. Data was analyzed using SPSS software version 17.0 software. Results: The mean pCO2 (27.95 ± 5.31mmHg) was much below normal range, and 91% of children had hypocapnia (pCO2 <35) after the febrile seizures. However alkalosis (pH > 7.45) was demonstrated in only 20% of children. Also pCO2 levels in samples drawn before 2 hours were significantly less than those taken after 2 hours (23.24 ± 3.44 vs 29.29 ± 4.99 respectively; p = 0.001). Conclusion: Our data indicates that febrile seizures may be associated with fever induced hyperventilation and ensuing hypocapnia may be one of the precipitating factor in inducing seizures. However, well-structured human trials are needed to demonstrate the same.

Keywords: Febrile seizures, hypocapnia, respiratory alkalosis, venous blood gas

Introduction: Febrile seizures (FSs) are one of the most common neurological illnesses in children aged 6 months to 5 years, with a cumulative incidence between 2% and 8%, depending on geographical and cultural factors.[1] Pathological mechanism that triggers FS is still not clear. FS pathophysiology is difficult to study because it mostly occurs at home, so there is access to only postictal data and physiological changes occurring during that period are missed.

Although a number of susceptibility genes and environmental factors have been identified, precise mechanism that triggers 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.[2]

Hyperventilation is a standard method to provoke absence seizures, supporting this hypothesis. Also, neuronal activity is strongly suppressed by various maneuvers that lead to decrease in brain pH.[3,4] Using an animal model of experimental FSs, it has been shown that hyperthermia causes respiratory alkalosis triggers seizures.[5] Moreover, these experimental FSs were completely and rapidly abolished by exposing the

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rat pups to 5% CO₂ in the air, suggesting a putative therapeutic regimen. There is paucity of data showing similar acid–base changes in human. This study was conducted to bring out any association of fever-induced respiratory alkalosis and induction of FS.

**MATERIALS AND METHODS**

This observational study was conducted at Dr. Ram Manohar Lohia Hospital and Post Graduate Institute of Medical Education and Research, New Delhi, India. Cases were enrolled after written informed consent were obtained from parents from November 2014 to March 2016. Study was approved by the institutional ethics committee. With reference to previous study, it was found that PCO₂ in patients with FS was 29.28 ± 7.30 mm Hg (mean ± standard deviation [SD]). Considering the same, sample size of 45 was calculated based on precision (allowable margin of error) of 30% of SD, at two-sided alpha of 0.05.

Children were enrolled after fulfilling predetermined inclusion and exclusion criteria. Children aged 6 months to 5 years with seizures in a setting of fever (temperature >37.8°C) not caused by meningitis, encephalitis, or any other illness affecting the brain, who are otherwise neurologically healthy with a normal neurological examination were included and those who presented 24 h after the onset of FS or on subsequent investigation found to be a case of meningitis were excluded. Children with lower respiratory tract infection were excluded as the results of blood gas analysis might be affected.

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 ice boxes. The level of blood gases (pCO₂) and pH was measured using Nova Biomedical pHOx plus L blood gas analyzer. Results were compared with standard values: pH, 7.35–7.45; pCO₂, 35–45 mm Hg; and base excess –2 to +2.

Axillary temperature was measured using a digital thermometer and the mean of two readings was taken. Patient characteristics such as age, gender, seizure type, degree, and duration of fever and seizures were also documented.

Descriptive statistics was analyzed with Statistical Package for the Social Sciences (SPSS), Inc. Version 17.0. Chicago. Continuous variables were presented as mean ± SD and categorical variables as frequencies and percentages. The Pearson’s chi-square test or Fisher’s exact test was used to determine the relationship between two categorical variables, whereas Student’s t test was applied for continuous variables. *P* value <0.05 was considered statistically significant.

**RESULTS**

Of 45 enrolled children, 29 were boys and 16 girls. The mean age of presentation was 22.87 ± 12.98 months and 77% of children were between 1–3 years. Approximately 84.4% were simple FS and remaining 15.6% were complex FS (including febrile status epilepticus). None of these children had a family history of epilepsy or FS. Average axillary temperature was 37.8°C with a range of 36.6°C–39.4°C. Majority (71.1%) of cases were attributed to upper respiratory

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**Table 1: Mean pH and pCO₂ levels in children with febrile seizures and their relation with time of onset of seizures**

| Blood gas parameter | VBG values (n = 45) | VBG values ≤2 h (n = 10) | VBG values >2 h (n = 35) | *P* value (<2 vs. >2 h) |
|---------------------|---------------------|--------------------------|--------------------------|--------------------------|
|                     | Mean ± SD | Min–Max | Mean ± SD | Min–Max | Mean ± SD | Min–Max | 0.209 |
| pH                  | 7.41 ± 0.04 | 7.32–7.50 | 7.43 ± 0.05 | 7.35–7.50 | 7.41 ± 0.04 | 7.32–7.49 | 0.209 |
| pCO₂ (mm Hg)        | 27.95 ± 5.31 | 14.8–39.6 | 23.24 ± 3.44 | 16.4–27.5 | 29.29 ± 4.99 | 14.8–39.6 | 0.001 |

VBG = venous blood gas

**Figure 1:** Difference in pH and pCO₂ in relation to the time of onset of febrile seizures

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**Table 2: Comparison of pCO₂ with axillary skin temperature**

| Temperature (°C) | Mean pCO₂ (mm Hg) | Min–Max | *P* value | <37.7°C vs. >37.7°C |
|------------------|-------------------|---------|-----------|----------------------|
| 36.6–37.7        | 28.97 ± 614       | 14.8–39.6 | 0.172 | 0.801 |
| 37.8–38.8        | 26.15 ± 3.37      | 21.4–34.4 |           |                      |
| >38.8            | 31.30 ± 3.82      | 28.60–34.0 |           |                      |
tract infections and the rest were due to acute gastroenteritis, urinary tract infections, otitis media, and enteric fever.

Venous blood gas analyses showed a mean pH of 7.41 ± 0.04 and a mean pCO$_2$ of 27.95 ± 5.31 mm Hg. The median pCO$_2$ was 26.80 mm Hg as shown in Table 1. To gain more insights of this association, we divided case into two groups depending on the time of presentation to hospital after seizure (≤2 h, n = 10 and >2 h, n = 35) as shown in Figure 1. The samples drawn within 2 h of seizure had a mean pCO$_2$ of 23.24 ± 3.44 mm Hg and those samples drawn after 2 h of seizure had a mean pH of 29.29 ± 4.99 mm Hg. The pCO$_2$ for the samples drawn in ≤2 h was lower than those drawn after 2 h and the difference was found to be statistically significant (P = 0.001).

Table 2 shows the relationship between changes in blood gases with change in skin temperature. In children with axillary temperatures recorded to be between 36.6°C and 37.7°C, the mean pCO$_2$ was 28.87 ± 6.14 mm Hg; in children with axillary temperatures recorded to be between 37.8°C and 38.8°C, the mean pCO$_2$ was 26.15 ± 3.37 mm Hg; and in children with axillary temperatures recorded to be >38.8°C, the mean pCO$_2$ was 31.30 ± 3.82 mm Hg. No statistically significant difference was found in pCO$_2$ with rising temperatures. We also compared children with simple FS and complex FS. No significant difference was found in either body temperature or pCO$_2$ level between these two groups.

**Discussion**

Fever is a direct cause of tachypnea in children. O’Dempsey et al.[9] measured a 3.7 breath per minute increase for every 1°C increase in body temperature in a large cohort of children. This rapid breathing leads to washout of CO$_2$ (hypocapnia), which in turn leads to respiratory alkalosis followed by brain alkalosis. Alkalosis is a known trigger of seizures.

We found that 91% of children had hypocapnia after FS. Cause of normal pCO$_2$ levels after FS in remaining 9% may be attributed to delay in bringing the child to hospital and thus delay in blood gas analysis. However, alkalosis (pH >7.45) observed in only 20% of children can also be attributed to delay in bringing the child to hospital and also to the fact that pH will normalize earlier than pCO$_2$ because of the presence of various buffers. We were also able to show a significantly (P = 0.001) higher pCO$_2$ levels in samples drawn after 2 h compared to those taken before 2 h, further proving that significant hypocapnia was present in samples taken just after FS episode, which then normalized with time and may have been a trigger for seizure activity.

In the study by Schuchmann et al.,[10] they compared patients with gastroenteritis and patients who had FS. Respiratory alkalosis was found in children with FS (pH, 7.46 ± 0.04; pCO$_2$, 29.5 ± 5.5 mm Hg), whereas metabolic acidosis was seen in children with gastroenteritis (pH, 7.31 ± 0.03; pCO$_2$, 37.7 ± 4.3 mm Hg; P < 0.001 for both parameters). So, the statistically significant difference may be attributed to the fact that children with gastroenteritis are as it is predisposed to metabolic acidosis because of bicarbonate losses in stool. Kilicaslan et al.[7] compared children with FS and children who presented with a febrile illness without seizures and found no significant difference in mean blood pH between FS and control groups but blood pCO$_2$ was significantly lower in FS group. However, it is a possibility that some children, especially the ones with FS, may be more genetically predisposed to hyperventilation and thus respiratory alkalosis compared to those who do not have FS. So, in our study, we compared the acid–base status of children presenting within 2 h and after 2 h of seizure episode but found results similar to the ones found in the study by Kilicaslan et al.[7]

Results of comparison of acid–base status in simple and complex FS group were contradictory in previous studies. In a study by Kilicaslan et al.,[7] complex FS group exhibited significantly lower pCO$_2$ levels than patients with simple FS, which was not shown in the study conducted by Schuchmann et al.[10] In our study, the mean pH and pCO$_2$ in children with simple FS and complex FS group was 7.41 ± 0.04 and 7.43 ± 0.03 and 27.78 ± 5.56 and 28.84 ± 3.85, respectively. No statistically significant difference was found (P = 0.222 and P = 0.633, respectively).

Our findings are in accordance with previous animal studies showing 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 hypocapnia increases spike trigger in hippocampus in both the in situ and in vitro population.[5,6] Schuchmann et al.[5] in 2006, using an animal model of experimental FS showed the same 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.[11] in 2005, showed activation procedures such
as hyperventilation 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.\textsuperscript{[3,6]} 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\textsubscript{2} and on the kidneys that control the excretion of bicarbonates.

Benzodiazepines are standard immediate treatment for the management of patient with febrile status epilepticus\textsuperscript{[12-14]} and were used similarly in our study subjects. They have broad spectrum of side effects such as hypotension, sedation, decreased alertness, and depressed respiratory effort in young child, which limits its clinical use. To overcome these therapeutic limitations, newer and safer treatment modalities are needed. CO\textsubscript{2} has been long recognized for its anticonvulsant properties. Animal studies where rat pups were exposed to 5\% ambient CO\textsubscript{2} suppressed the experimental FS with a delay of only 20 s. In a pilot trial carried out in seven patients, a rapid termination of electrographic seizures was seen.\textsuperscript{[6]}

This study concludes that FS may be associated with respiratory alkalosis and might be one of the precipitating factors in genetically susceptible children. This study design has inherent limitations that FS occurs mainly at home, hence there is only access to postictal data, and crucial period of acid–base derangement during pre-ictal phase or ictal phase is difficult to study. Another limitation of this study was a small sample size, especially those children who are presenting to the emergency unit within 2 h. Although these data are insufficient to show strict causal relationship between hypocapnia and FS, they give sufficient background knowledge to design for subsequent clinical trials and novel therapies aimed at suppressing FS.

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Conflicts of interests
There are no conflicts of interest.

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