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Original Research Article

A comparative study of serum zinc levels in children with febrile seizures and children with fever without seizures in an urban referral hospital

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ABSTRACT

Background: Febrile seizures are the most common cause of convulsions in children. However, the exact underlying etiology and the pathophysiological mechanisms are yet to be established. Various theories have been put forward regarding the role of trace elements as predisposing factors in causing the convulsions. Among them, Zinc is the most interesting trace element whose role in diarrhea and pneumonia is well proven. This study was done to know the correlation between zinc and febrile seizures, to estimate the serum levels of zinc in children with simple and complex febrile seizures and compare it with children with fever without seizures and to compare the levels of zinc in simple and complex febrile seizures.
Methods: The study was conducted for a period of 6 months in the Department of Paediatrics, GMKMCH, and Salem. The study population included the children between 6 months to 6 years. During the study period 60 consecutive children with simple febrile seizures, 40 consecutive children with complex febrile seizures and 200 consecutive children with fever without seizures formed the study group. Serum zinc levels were measured in the three groups by using the calorimetric method.
Results: The serum zinc levels were found to be low in 65% and 75% of children with simple and complex febrile seizures respectively. Only 20% of febrile children without convulsions had low zinc levels. Thus, a positive correlation was found between zinc deficiency and febrile convulsions.
Conclusions: This study establishes a definite relationship between zinc deficiency and febrile seizures thereby substantiating zinc as an important predisposing factor in febrile seizures.

Keywords: Complex febrile convulsions, Fever, Simple febrile seizures, Zinc

INTRODUCTION

Febrile seizures occur in young children at a time in their development when seizure threshold is low. They typically occur relatively early in an infectious illness usually during the rise of temperature curve.[1] Febrile seizures occur in common childhood infections such as infections of the respiratory system, otitis media, acute gastroenteritis, and children respond to these infections with comparably higher temperatures.[2] The onset of febrile seizures generally follows a bell-shaped curve. 94% occur within the first three years of age and 6% after three years of age. Approximately one half appears during second year of life with peak incidence between

18 to 22 months. Febrile seizures occurring before 6 months should raise the suspicion of serious infections like bacterial meningitis.[3] Genetics have a definite contribution in febrile seizures. The empiric chance after one child is affected is 10%; it rises to almost 50% if one parent had febrile convulsion. However the exact mode of inheritance is not completely understood. Most studies suggest a dominant mode of inheritance with reduced penetrance. Linkage studies in various chromosomes have mapped the gene to chromosome 19p and 8q 13-21.[4] The incidence in India varies between 3-5%.[5] Many studies show a slight male preponderance. A number of trace elements are said to play a role in febrile convulsions by their co-enzyme activity or ability to influence ion channels and receptors. Studies have shown that iron, zinc, selenium, copper and magnesium play a significant role in febrile convulsions. Neurons rich in zinc carry the element in their synaptic vesicles. They are a special group of neurons.[6]

Zn is as a co-factor of glutamate decarboxylase which is an enzyme needed for gamma-aminobutyric acid synthesis in the central nervous system and reduced CSF zinc levels have also been noted in febrile convulsions. Recent evidences indicate that zinc deficiency plays a significant role in febrile seizures. The following mechanisms can be postulated. Zinc increases storage capacity of glutamate or slows down the release rate of glutamate.[7] Zinc increases the activity of pyridoxine needed for pyridoxine formation reciprocally pyridoxine increases the activity of glutamate decarboxylase which results in gamma-aminobutyric acid syntheses. Thus, decreased zinc levels lowers GABA synthesis which would precipitate seizures.[8] Persistent and prolonged seizure activity cause cerebral edema, hypoxia, hyperthermia, hypoglycemia and vasomotor instability. respiratory depression may ensue from involvement of respiratory centre or from drugs used for seizure control. Vomiting and aspiration of secretions also increase morbidity. Hence treatment should be taken precedence over investigation of the cause.[9]

Zinc plays an important role in tissue or cell growth. This is related primarily to its function in the regulation of protein synthesis as well as synthesis and catabolism of nucleic acids. With respect to transcription, zinc appears to interact with nuclear proteins that bind to promoter sequences of specific genes, zinc forms a structural component of zinc fingers which recognize DNA base sequences during replication and transcription of DNA.[10]

METHODS

the cross-sectional study was conducted period from Government Mohan Kumar Mangalam Medical College and Hospital Salem for 6 months in the year 2017. Sample size of 300 in the three groups.

- Group 1: Children with simple febrile seizures
- Group 2: Children with complex febrile seizures
- Group 3: Children with fever without seizures.

Inclusion criteria

- Children aged six months to six years with simple febrile seizures
- Children aged six months to six years with complex febrile seizures
- Children aged six months to six years with fever without seizure.

Exclusion criteria

- Cerebral palsy
- Seizure disorder
- Chronic illness
- Dysmorphic features
- Children on zinc supplementation
- Children on antiepileptic drugs.

Informed consent was obtained from the parents of all the children included in the study group in a written consent form. All queries regarding the study were cleared and signature of the parent was obtained. The study protocol was approved by the ethical committee of our government hospital on 06/12/2017. Prior to inclusion in the study, a detailed history of presenting complaints was recorded including the duration of fever, type of seizures, duration of seizures, family history of seizures. In addition, history suggestive of fever etiology cough, cold, nasal discharge, ear discharge, burning micturition or crying during micturition, breathing difficulty were also recorded.

Vitals signs namely heart rate, respiratory rate, capillary refilling time and blood pressure were recorded. The axillary temperature was recorded in all children with mercury thermometer positioned in the axilla placed for three minutes. Anthropometric measurements namely weight, height, mid-arm circumference and head circumference were recorded for the nutritional status. This was followed by general examination and systemic examination of the central nervous system in detail. Those children who showed features of any chronic congenital or acquired illness were excluded.

Those who showed features of intracranial infection like altered sensorium, neck stiffness, bulging anterior fontanel etc were also excluded. During the study period 60 consecutive children with simple febrile seizures, 40 consecutive children with complex febrile seizures and 200 consecutive children with fever without seizures formed the study group. This was based on the annual morbidity pattern in our hospital. Two milliliters of whole blood was collected by venipuncture under strict aseptic precautions and sent to biochemistry laboratory for assessment of serum zinc levels. Determination of serum zinc levels was done by calorimetric method. The principle being zinc in alkaline medium reacts with nitro PAPS to give a purple color change. The intensity of the

color formed depends in a direct relation to the levels of zinc found in the sample. Though earlier studies have established a linear relationship between serum zinc and CSF zinc in children with febrile seizures, CSF zinc analysis was not done in our study and based on ethical grounds. CSF analysis as done in all cases of febrile seizures under 1 year and in all children with complex febrile seizures. CT brain and EEG were done in cases of complex febrile seizures. Complete blood count, urine analysis, chest X-ray were carried out to identify the etiology of fever

Statistical analysis

The Statistical software namely SAS 9.2, SPSS 11.5, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver. 2.11.1 were used for the analysis of the data and Microsoft Word and Excel have been used to generate graphs, tables etc.

RESULTS

In the simple febrile convulsions group 11 of children were below 1 year, 30 of them were between 1-2 years, 11 were between 2 to 3 years, 2 between 3 to 4 years and 6 of them were between 4 to 6 years of age which accounts to 33%, 70%, 33%, 6%, 6% and 12 % respectively. In the complex febrile convulsions group 12 of children were below 1years of age, 11 were between 1 to 2 years, 3 were between 2 to 3 years and 6 between 4 to 6 years of age which accounts to 36%, 30%, 9%, 12%, 6%, and 12% respectively. In the fever group 42 of children were between 6 months to 1 year, 54 were under 2 years of age, 42 children between 2 to 3 years, 24 were between 3 to 4 years and 24 between 4 to 5 years of age and 14 of them were between 5-6 years which accounts to 127%, 163%, 127%, 42%, 72% and 42% respectively.

Table 1: Age distribution between 3 groups.

Age in years	Children wit simple febril convulsions		Children with complex febrile convulsions		Children with fever without seizures	
	No.	%	No.	%	No.	%
6 months 1 year	11	33.3	12	36.4	42	127.3
1 - 2 years	30	90.9	11	33.3	54	163.6
2 - 3 years	11	33.3	3	9.1	42	127.3
3 - 4 years	2	6.1	4	12.1	24	72.7
4 - 5 years	2	6.1	2	6.1	24	72.7
5-6 years	4	12.1	4	12.1	14	42.4
Total	60	181.8	40	121.2	200	606.1
P value	0.148	Chi-square				

There is a statically significant difference in the distribution of upper respiratory illness as the cause of fever among the children with simple and complex febrile convulsions. Viral fever predominates in the children only with fever. The percentage of distribution of URI is 38.2%, 45.3% and 12% among the simple, complex febrile convulsions and only fever group respectively accounts to 23, 18 and 24 cases respectively. Viral fever was the second most common cause of illness among the convulsions groups seen in 20.6%, 17.2% and 30.6% is seen in the only fever group which accounts to 13, 7 and 60 cases respectively.

Table 2: Focus of infection.

focus of infection cause	Children with simple febrile convulsions		Children with complex febrile convulsions		Children with fever without seizures		P-value
	No.	%	No.	%	No.	%	
Age	8	13.3	0	0	0	0	0.015*
Acute orithits media	5	8.3	4	10.0	0	0	0.203
Enteric fever	0	0	0	0	26	13.0	0.015*
Lower respiratory tract infection	2	3.3	7	17.5	36	18.0	0.109
Malaria	0	0	0	0	6	3.0	0.370
Pharyngitis	0	0	0	0	18	9.0	0.045*
Upper respiratory tract infection	23	38.3	18	45.0	24	12.0	0.009*
Urinary tract infection	9	15.0	4	10.0	30	15.0	0.702
Viral fever	13	21.7	7	17.5	60	30.0	0.479
Total	60	100.0	40	100.0	200	100.0	

Acute gastroenteritis is seen in 11.8% i.e., 8 cases in category of simple febrile convulsions and enteric fever is seen in 11.1% of cases in the only fever group which accounts to 30 cases.

The percentage of acute otitis media in the 3 groups are 8.8%, 6.9% and 2.8% involving 5 and 4 children respectively. LRI is found in 5.9%, 17.2% and 16.7% respectively among the 3 groups as the cause of fever

accounting to 2, 7 and 36 cases respectively. Malaria and pharyngitis was diagnosed in 2.8%, 6 cases and 8.3% i.e., 18 of children who presented only with fever. Urinary tract infection was the etiology of fever in 14.7%, 10.3% and 13.9% of children accounting to 9, 4 and 30 cases respectively.

Table 3: Range of temperature between 3 groups.

Temperature range	Children with simple febrile convulsions		Children with complex febrile convulsions		Children with fever without seizures		P value
	No.	%	No.	%	No.	%	
100-100.9 F	28	46.7	20	50.0	126	63.0	0.307
101-101.9 F	28	46.7	14	35.0	44	22.0	
102-103 F	4	6.7	6	15.2	30	15.2	
Total	60	100.0	40	100.0	200	100.0	

In the group of simple febrile convulsions, 28 had 100-100.9, 28 cases had 101-101.9 F and 4 children had 102-103 accounting to 45%, 48% and 6% respectively. In the atypical convulsions group, 20, 14 and 6 children had temperature ranges of 100-100.9, 101-101.9 and 102-103 accounting to 51%, 33% and 15% respectively. In the fever group, 126, 44 and 30 children recorded the respective temperatures attributing to 63%, 21% and 15%. From Table 3, it is evident that the children with lower zinc levels are more prone to develop febrile seizures even at lower temperature ranges.

Table 4: Zinc levels in children studied.

Zn level (microgram/dl)	Children with Simple febrile convulsions		Children with complex febrile convulsions		Children with fever without seizures		P-value
	No.	%	No.	%	No.	%	
Low	39	65.0%	30	75.0%	40	20.0%	0.002**
Normal	21	35.0%	10	25.0%	160	80.0%	
Total	60	100.0%	40	100.0%	200	100.0%	
Mean±SD	57.69±9.46		60.66±11.33		73.12±15.15		

Mean ZINC levels are significantly less in children with Complex febrile convulsions followed by Children with simple febrile convulsions. Correlation between the zinc and the 3 study groups:

- Simple febrile versus fever without seizures P <0.002 (significant)
- Complex febrile versus fever without seizures P <0.002 (significant)
- 3.Simple febrile versus complex febrile P = 0.700 (not significant).

Normal reference range of zinc values: 60-150 microgram/dl. Serum zinc levels were found to be low in 39 children with simple febrile seizures which accounts for 65%. Serum zinc levels were found to be low in 30 children with complex febrile seizures that accounts for 75%. Serum zinc levels were found to be low in 40 febrile children without seizures accounting to 20%. Thus, there is a statistically significant difference in the serum zinc levels measured in the children with simple and complex febrile seizures in comparison to febrile children without seizures. However, though serum zinc levels were found to be lower in simple febrile convulsions than complex febrile convulsions, statistically there was no significant difference between the two groups.

DISCUSSION

Febrile seizure is a common neurologic problem occurring in children aged between 6 months to 6 years. The etiology of febrile seizure is unknown but genetic factors or electrolyte disturbances may have a role in its occurrence or recurrence.[11] To date, it is revealed that febrile seizures can be induced by several factors. There is a hypothesis that febrile seizures arise due to excitation of the neurons during brain growth. This correlates with the most common age group in which this entity occurs. Gamma-aminobutyric acid is an important inhibitory neurotransmitter.[12] Zinc has a regulatory effect on glutamic acid decarboxylase and the synthesis of GABA.

Attempts have been made to identify predisposing risk factors like family history, metabolic disturbance (especially serum zinc, magnesium, glucose, calcium). This knowledge has a practical value in advising parents regarding recurrent convulsions.[13] The mean serum zinc levels in the present study in simple and complex febrile convulsions and in fever alone without convulsions were 57 microgram/dl, 60 microgram/dl, and 73 microgram/dl respectively.

Children with febrile convulsions both simple and complex have statistically significant low serum zinc levels when compared to children with fever alone without convulsions. Children with fever alone did not show a decrease in serum zinc level compared to other groups which are similar to findings of other studies.[14] Also there was no significant difference in serum zinc levels between simple and complex febrile convulsions. Hauser et al compared 50 cases of simple and complex febrile seizures each with a control which showed significant low zinc values in seizure group ($p<0.002$).[15] Engel L et al in his study zinc values was significantly lower in cases compared to controls with a p value<0.05.[16]

Hitz et al conducted a study comparing both serum and CSF zinc levels in febrile seizures with nonconvulsive fever group.[17] He showed a statistically significant difference of p value <0.001. Ganesh et al from Chennai, Lee et al, and Hitz et al also showed similar results.[18] The serum zinc levels did not show any significant correlation with age of onset, gender, family history and nutritional status in this present study. All previous studies have shown similar findings in this aspect. As serum zinc concentration in any population is influenced by factors such as dietary pattern, vitamin A, vitamin D deficiency, zinc levels in the soil and water, further studies are needed in this aspect to identify the probable cause for this finding.[19, 20]

CONCLUSION

The present study has shown that zinc deficiency is one of the predisposing factors for simple and complex febrile convulsions thereby making a small contribution to the medical literature by strongly establishing the relationship between zinc deficiency and febrile seizures. Also, the significant proportion of children (20%) in the group of fever without seizures in the study population are vulnerable to develop febrile seizures and needs zinc supplementation. Future research should be directed towards the therapeutic trial of zinc supplementation and formulate the zinc treatment regimen including its dose and duration.

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