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Correlation of Serum Zinc Level with Simple Febrile Seizures: A Hospital based Prospective Case Control Study

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Abstract

Introduction

Febrile seizures are one of the most common neurological conditions of childhood. It seems that zinc deficiency is associated with increased risk of febrile seizures. The main purpose of the study is to estimate the serum Zinc level in children with simple febrile seizures and to find the correlation, if any between serum zinc level and simple febrile seizures.

Materials and Methods

The proposed study was a hospital based prospective case control study which included infants and children aged between 6 months to 5 years, at Post Graduate Department of Pediatrics, (SMGS) Hospital, GMC Jammu, Northern India. A total of 200 infants and children fulfilling the inclusion criteria were included. Patients were divided into 100(cases) in Group A with simple febrile seizure and 100(controls) in Group B of children with acute febrile illness without seizure. All patients were subjected to detailed history and thorough clinical examination followed by relevant investigations.

Results

Our study had slight male preponderance of 62% in cases and 58% in controls. Mean serum zinc level in cases was 61.53±15.87 ugm/dl and in controls it was 71.90+18.50 ugm/dl. Serum zinc level was found significantly low in cases of simple febrile seizures as compared to controls ($P<0.05$).

Conclusion

The presence of biochemical hypozincemia, associated with other risk factors for simple febrile seizures may enhance the occurrence of febrile seizures, thus a possible correlation exists between the mean serum zinc level and simple febrile seizures.

Key Words: Children, Febrile seizures, ILAE, Serum zinc levels.

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Introduction

International League Against Epilepsy (ILAE) has defined an epileptic seizure as transient occurrence of signs and or symptoms due to abnormal, excessive or synchronous neuronal activity in the brain. Febrile seizures are seizures that occur between the age of 6 and 60 months with a temperature of 38°C or higher, that are not the result of central nervous system infection or any metabolic imbalance, and that occur in the absence of a history of prior non-febrile seizures (1). Various factors have been described in the pathophysiology of febrile seizures like bacterial and viral infections (2), susceptibility of the immature brain to temperature (3), association with interleukins (4), circulating toxins (5), trace element deficiency (6) and iron deficiency **(7)**. Role of trace elements like selenium, magnesium, copper and zinc have been described in association with febrile seizures (7). Trace elements appear to play a role by their ability to modulate neurotransmission by acting on ion channels and their coenzyme activity.

Zinc is an important element in growth, development and normal brain function. It is also an important cofactor for different enzymes, is involved in cellular growth and differentiation, enzymatic activity of different organs, proteins and cellular metabolism. In brain, zinc is present in synaptic vesicles in subgroup of glutaminergic neurons. In this form it can be released by electrical stimulation and may serve to modulate responses at receptors level. These include both excitatory and inhibiting receptors particularly N-Methyl-D aspartate (NMDA) and Gamma aminobutyric acid (GABA) receptors respectively (8, 9).

Decreased zinc levels modulates the activity of glutamic acid decarboxylase, the rate limiting enzyme in the synthesis of Gamma Amino Butyric Acid (GABA), which is a major inhibitory neurotransmitter (8). Any abnormalities of GABAergic function, including synthesis, synaptic release, receptor composition, trafficking or binding, and metabolism, can each lead to a hyperexcitable, epileptic state (9, 10). Zinc has an inhibitory effect on N-Methyl-D aspartate receptors**,** which is responsible for excitatory phenomenon after binding with glutamate. Thus decreased Zinc levels may play a role in pathogenesis of febrile seizures. Previous studies have reported the low serum zinc level in children with febrile seizures (11-15). The present study intends to estimate the serum zinc levels in children with febrile seizure and acute febrile illness without seizure and to correlate the serum zinc level with simple febrile seizures.

Materials and Methods

The proposed study was a hospital based prospective case control study with RCT code of AEARCTR-0000631 which included infants and children aged between 6 months to 5 years, at Post Graduate Department of Pediatrics, Shri Maharaja Gulab Singh (SMGS) Hospital, Jammu, Northern India (Picture.1).

All patients whose parents/guardians have consented for the study and had simple febrile seizure, normal development, age between 6 months and 5 years were included as cases and patients with complex febrile seizure, age younger than 6 months and older than 5 years, history of recent zinc intake, developmental delay and or neurologic deficit, malnutrition, acute and chronic diarrhea, electrolyte imbalance were excluded from the study. The axillary temperature was recorded in all children with mercury thermometer placed in axilla for three minutes, followed by general examination and systemic examination in detail.

Taking all aseptic precautions, 2 ml of blood from venipuncture using 22 gauge sterile needle, within 24 hours of contact of patient in both the groups. The

sample was centrifuged for 3-4 minutes at 3,000-4,000 rpm, serum thus obtain and preserved in sterile deionized vial. Estimation of serum zinc was done within 6 hours of collection. Method used was based on colorimetric test kits, reagent used was 2-(5-bromo-2-pyridylazo)-5-(N-propyl-N-sulphopropylamino) phenol. Zinc forms a red chelate with it. Increase in the absorbance of wavelength 560 nm can be measured and is proportional to concentration of the zinc.

Picture.1: Jammu and Kashmir, Northern India

Statistical analysis

Data was analyzed using MS Excel SPSS version 17.0 for windows. Zinc level presented as mean and standard deviation, the difference in mean among the groups was assessed by use of one way ANOVA followed by post hoc bonferronis t-test to analyze inter group difference. Correlation was analyzed with relevant statistical method. Correlation co-efficient was calculated. A p- value less than 0.05 was taken as statistically significant.

Results

Table.1, represents the mean age of group A and group B. Mean age were nearly similar in the both Groups. Table.2, represents the gender distribution of population of and shows that males predominated in both the groups (P=0.683).

Table 1: Age group distribution of group A & group B

Age Group(months)	Group A(cases) =100		Group B (controls) =100	
	No	%	No	%
6-12	36	36%	28	28%
13-24	35	35%	39	39%
25-36	15	15%	23	23%
37-48	8	8%	5	5%
49-60	6	6%	5	5%

Table 2: Gender distribution of Group A & Group B

Gender	Group A (cases) n=100		Group B (controls) n=100	
	N	%	N	%
Male	62	62%	58	58%
Female	38	38%	42	42%
Total	100	100%	100	100%

Table.3, represents the distribution of diagnosis in group A and group B and shows that non localized fever(viral) predominated as the cause of fever in the both groups, followed by ARI and ASOM. Table.4, represents the mean serums zinc level in the both groups. Mean serum zinc level was 10.45 ugm/dl less in cases of simple febrile seizure as compared to controls (P<0.005). Table.5 represents the number of patients in both groups with bio-chemical hypozincemia and shows that 60% of the cases and 34% of the controls had bio-chemical hypozincemia (P=0.001).

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Table 3: Distribution of diagnosis in Group A and Group B

Daignosis	Group A (cases)		Group B (controls)	
	No.	%	No.	%
ARI (Acute respiratory infections**)**	20	20	42	42
Non localised fever (viral)	60	60	46	46
UTI (Urinary tract infection)	5	5	4	4
ASOM (Acute suppurative otitis media)	10	10	5	5
Bronchiolitis	5	5	3	3
Total	100	100	100	100

Table 4: Comparison of mean serum Zinc level between group A and group B

Variables	Serum Zinc level (ugm/dl)	Mean difference	P-value
Group A	61.53±15.87	-10.45	<0.05
Group B	71.90+18.50		

Table 5: Comparison of Zinc deficiency among group A and group B

Zinc level	Group A		Group B		Total	
	No.	%	No.	%	No.	%
<65 µgm/dI	60	60	34	34	94	47
>65 µgm/dI	40	40	66	66	106	53
Total	100		100		200	

Discussion

Zinc is an essential micronutrient required for the normal function and development of the central nervous system. It has a role in modulation of neurotransmission by inhibitory effect on the Glutaminergic NMDA receptor, and by acting as a cofactor to the rate limiting enzyme in GABA synthesis.

Hence its deficiency can lead to the excitation inhibition imbalance precipitating a febrile seizure. Few authors have studied the relationship between serum zinc level and simple febrile seizures, majority of which support the association of hypozincemia with simple febrile sizures, on the contrary few do not. The present study was under taken in this context to study the correlation of serum zinc level with simple Febrile seizures.

More than two third of the patients were below 2 years with mean age of 22.72 and 25.67 months in cases and controls respectively.

Mean age in cases falls within the range of mean age of (21-27 months) as reported by others (12, 16-20). Males predominated in present study with male female ratio of 1.63:1.This was similar to the gender ratio ranging from (1.4-1.7):1 as reported by (6, 11, 12, 16-20). Family history of seizures

was present in 9%, 6% had history of simple febrile seizures in the first degree relatives and 3% had history of epilepsy in family; while among 3% patient with family history of epilepsy 2% had history in first degree and 1% had history in second degree relative. Similar findings were reported by Guzman et al. (21) whom reported family history in 10% of patients. However Kumari, Margaretha and Kafadar (7,12,19) reported family history in 44.4%, 48%, 26% of patients respectively. The clinical presentation comprised of mainly non localized fevers majority of which had clinical evidence to suggest viral etiology (60%), followed by ARI (20%), ASOM (10%), UTI (5%) and bronchiolitis (5%). Margaretha and Günduz (12,22) have reported ARI as most common cause Majority of the authors who have correlated serum zinc level with simple febrile seizure have studied this correlation by compairing mean serum zinc level between cases and controls, while few others studied this correlation by determining the number of patients having hypozincemia in subject population. Data was analyzed in the present study by both these methods. As per World Health Organization (WHO) recommendation the cut off value for hypozincemia has been taken as 65µgm/dl (23). Hence 65µgm/dl was taken as cutoff for hypozincemia as suggested by WHO. Hypozincemia was present in majority of the patients (60%), though no statistical significant difference was found in the mean age, gender distribution, physical parameters, and nutritional status between the patients of hypozincemia and normal zinc level. Mahyar et al. were reported the similar findings (18) (Table.6).

Table 6: Mean serum zinc levels obtained in various studies

Studies	Serum Zinc level(µgm/dl)		Mean Difference	P-value
	Cases	Control		
Ganesh R et al. (16)	32.17	87.60	55.43	<0.001**
Okposio et al. (24)	58.70	90.30	31.6	<0.001**
Mahyar et al.(18)	62.84	85.7	22.86	<0.05*
Burhangnoglu (25)	66.00	98.00	32	<0.05*
Amiri et al.(6)	66.13	107.8	41.67	<0.05*
Heydarian F (17)	66.37	75.83	9.46	<0.001**
Ehsani et al. (11)	76.80	90.12	13.32	< 0.05*
Margaretha (12)	88.30	137.20	48.9	<0.001**
Modarresi et al. (26)	93.39	130.54	37.15	<0.001**
Kafadar et al. (19)	110.49	107.12	-3.37	0.673
Talebian et al. (20)	116.28	146	29.72	<0.05*
Present Study	61.53	71.99	10.46	<0.05*

*Significant **Highly significant

In the present study significant difference of 10.46 µg/dl was obtained in mean serum zinc level in cases as compared to controls. Similar findings have been reported by other researchers (6, 11-18, 20, 25) as shown in (Table.6). The present study also did not reveal any significant difference in mean serum zinc level in relation to age groups or gender. Similar findings were reported by other researchers (16, 19, 20, 25). Thus the present study reveals that no specific age group or gender is particularly predisposed to develop hypozincemia.

Hypozincemia was observed to be more frequent in children with simple febrile seizures in the present study. Clinical presentation of those patients with biochemical hypozincemia did not differ from those with normal zinc levels. No classical clinical manifestations of hypozincemia as mentioned in literature like diarroea, impaired appetite, decreased growth velocity, acro orificial skin lesions, delayed wound healing, dysgusia and hypogusia were present in the patients of hypozincemia. Neither these patients had any predisposing conditions associated with hypozincemia like Acrodermatitis enteropathica, recent gastrointestinal tract infection, malabsorption, chronic liver disease or chronic illness. Hence most of these patients had purely biochemical hypozincemia.

Conclusion

Thus it appears that presence of hypozincemia in presence of other risk factors of febrile seizures may enhance the occurrence of febrile seizures explaining a possible correlation between low serum zinc levels and simple febrile seizures. However, large randomized control trials are recommended to analyze this association and if proven, the possibility of prophylactic zinc supplementation in reducing the risk of febrile seizures in such patients.

Conflicts of interest: None.

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