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RESEARCH ARTICLE

IMPLICATIONS OF ALTERATION OF SERUM TRACE ELEMENTS IN FEBRILE SEIZURES

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ABSTRACT

Introduction: Febrile seizures is the most common type of seizure in infancy and childhood. Its pathogenesis is still ambiguous. Changes in serum levels of trace elements have been proposed to underlie febrile seizures.
Aim: To determine implication of serum magnesium and zinc levels in the pathogenesis of febrile seizures.
Method: This prospective, analytical, case control study was carried out from October 2015 to September 2016 on 164 pediatric population aged between 6 months to 5 years admitted in JSS hospital, Mysuru. 82 cases of febrile convulsions and 82 age matched controls (with fever and no convulsions) were taken for the study. Serum magnesium levels were estimated by Xydiyl blue method and serum Zinc by calorimetric method in fully automated chemistry analyzer. Data was statistically analyzed using independent t- test and Chi- square test. SPSS version 21.0 is used for all calculations
Results: Mean serum zinc levels were 8.93± 2.01 µmol/Land 12.74±3.47 in cases and controls respectively. Mean serum magnesium levels in cases and controls were 2.13± 0.46 mg/dl and 2.61± 0.54 respectively. Both the differences were statistically significant.
Conclusion: Our study infers that deficiency of trace elements may be significantly related to the risk of febrile seizures in children.

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INTRODUCTION

Febrile seizures are a common paediatric emergency. They are the most common type of seizure in children aged between 5 months to 6 years constituting 30% of all seizure types (Vestergaard *et al.,* 2006). ILAE defines febrile seizures as ''a seizure occurring in childhood after one month of age, associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures'' (ILAE, 1993). It occurs usually below 3 years of age, with maximum at the age of 18 months (Shinnar, 2003). The Cumulative incidence reported in India is between 5-10%.[4]Though considered benign, a small percentage of children with febrile seizures may have recurrence and it may be a precursor for epilepsy. Despite the high clinical burden of febrile seizures, little advance has been made in understanding its aetiology. Family history of febrile seizures is a strong predictor for its occurrence.

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Studies have shown that suboptimal brain function in case of neonatal intensive care graduates with prematurity or low birth weight may increase the risk of febrile seizures. Any bacterial or viral infections can be a trigger for febrile seizures especially HHV-6 infection (Hauser, 1994; Frantzen *et al.,* 1970; Waruiru and Appleton, 2004). Trace elements like zinc, magnesium, iron, selenium by virtue of their role in membrane stabilization, neurotransmission, enzymatic activity and excitability have been implicated in the aetiology of febrile seizures by number of studies. Hence our study was conducted to look for any implications of alteration of serum trace elements (Zn and Mg) in febrile seizures.

MATERIALS AND METHODS

This prospective, analytical, case control study was carried out from October 2015 to September 2016 on 164 pediatric population aged between 6 months to 5 years admitted in JSS hospital, Mysuru. 82 cases of febrile convulsions (simple and complex) and 82 age matched controls (with fever and no convulsions) were taken for the study. Children with history of congenital anomalies of CNS, neonatal seizures, neuro infection and other metabolic conditions causing seizure and

those who received Zinc and Magnesium supplements were excluded from study. This study was approved by the institution ethical committee. All the patients received emergency intervention. Detailed history was taken and routine investigations were performed. Parents/guardians were informed about the study and consent was taken. With all aseptic precautions 3ml blood was collected in plain vacutainer and was centrifuged. The serum obtained was then estimated for Magnesium and Zinc levels. Magnesium was estimated by Xydiyl blue method in fully automated chemistry analyzer Toshiba- TBA 120 FR. Zinc was estimated by calorimetric method in fully automated chemistry analyzer Randox- RX imola. Normal serum Magnesium level is 1.7-2.7 mg/dl and serum Zinc level is 9.18-18.4 µmol/l. The descriptive statistics was done by measuring proportions, mean and standard deviation. Inferential statistics was done using chi-square test and independent t test. The p value <0.05 is considered as statistically significant. SPSS version 21.0 is used for all calculations.

RESULTS

62.2% of the cases were males and 37.8% were females. Mean age group of study population was around 30 months with 64.6% of febrile seizures below the age of 3 years (table 1, 2). In majority of cases cause of fever was respiratory tract infections (36.6%).

Table 1. Gender distribution between cases and controls

		Controls		Cases		p
		n	%	n	%	
SEX	Female	39	47.6	31	37.8	0.2
	Male	43	52.4	51	62.2	

Table 2 Comparing age (Mean ± SD) between cases and controls

	Controls			Cases			
	Mean	SD	Median	Mean	SD	Median	p
Age in months	29.2	18.2	25.0	30.0	19.1	25.0	0.8

Table 3. Family history of febrile seizure(n) in cases and controls

		Group			
		Controls		Cases	
		N	%	n	%
Family history of febrile seizure	No	73	89.0	51	62.2
	Yes	9	11.0	31	37.8

Family history of seizures was found in 31% of cases and 11% of controls (Table 3)

Table 4. Comparing levels of Magnesium and Zinc (mean±sd) between cases and controls

	Controls		Cases		
	Mean	SD	Mean	SD	P
Magnesium mg/dl	2.61	0.54	2.13	0.46	<0.001
Zinc µmol/L	12.74	3.47	8.93	2.01	<0.0001

Mean serum Magnesium levels were 2.61± 0.54 and 2.13± 0.46 in controls and cases respectively. Mean serum Zinc levels were 12.74± 3.47 and 8.93± 2.01 in controls and cases respectively. Both the differences were statistically significant (Table 4).

Table 5. Comparison of hypomagnesemia and hypozincaemia between cases and controls

		Group				
		Controls		Cases		
		N	%	N	%	P
Hypomagnesemia	No	80	97.6	68	82.9	0.002
	Yes	2	2.4	14	17.1	
Hypozincaemia	No	71	86.6	33	40.2	<0.0001
	Yes	11	13.4	49	59.8	

14 cases and 2 controls had low magnesium levels. 49 cases and 11 controls had hypozincaemia. Both the differences were statistically significant (Table 5).

DISCUSSION

Most febrile seizures occur between 6 months and 3 years of age with the peak incidence at 18 months. Approximately 6–15% occur after 4 years, and onset after 6 years is unusual (Hauser , 1994; Offringa *et al.,* 1991). 64.6% of febrile seizure children in our study were below 3 years. Male preponderance was seen in our study. Forsgren L *et al* had reported high incidence of febrile seizures in males (Forsgren *et al.,* 1990). However several other studies didn't observe any significant gender difference (Verity*et al.,* 1985; Fahimeh *et al.,* 2009). Family history of febrile seizures was present in 31% of cases in our study. Hauser WA *et al* and Frantzen *et al* found out positive family history of febrile seizures in 25-40% of cases when a child presents with a Febrile seizure (Hauser, 1994; Frantzen *e al.,* 1970). Most common cause of fever in our study was respiratory tract infections. Febrile seizures are more likely to occur with respiratory illness than with gastrointestinal illness although any infection can provoke the episode (Kaputu Kalala Malu *et al.,* 2013).

Magnesium is the second most abundant intracellular cation and is critical to the function of basically every organ in the human body (Ebel and Gunther, 1980).

Magnesium is implicated in anticonvulsant action by its anti-excitatory effect exerted by various mechanisms like NMDA receptor blockade thereby antagonising effects of glutamate, voltage gated calcium channel blockade leading to decreased release of glutamate from presynaptic neurons and stimulation of $GABA_A$ receptors with resultant hyperpolarisation of neurons (Mayer *et al.,* 1998; Iseri and French, 1984). Chhaparwal *et al* found out that serum levels of Magnesium were significantly low among children with febrile seizures than that of normal children in same region, boosting the hypothesis "Hypomagnesemia may be related to occurrence of febrile seizures" (Chhaparwal *et al.,* 1971). Later on, studies by Ahmad Talebian *et al*, Papierkowski A *et al*, Sreenivasaiah Bharathi *et al* strengthened this association (Ahmad Talebian *et al.,* 2009; Papierkowski *et al.,* 1999; Sreenivasaiah Bharathi and Kotte Chiranjeevi, 2016). In our study, we observed that mean serum levels of magnesium were significantly low in febrile seizure group when compared with controls. Also, statistically significant hypomagnesemia was seen between cases and controls. This is in accordance in aforementioned studies. Zinc is an essential trace element for humans.

It is found in nearly 300 specific enzymes, serves as structural ions in transcription factors and is stored and transferred in metallothionein (Maret and Wolfgang, 2013; Plum *et al.,* 2010).

Free zinc is largely localized to the presynaptic vesicles of glutamatergic neurons. Mossy fibres of hippocampus, the amygdala, the olfactory bulband cerebral cortex are rich in vesicular free zinc (Franco-Pons *et al.,* 2000; Frederickson *et al.,* 2000). Synaptic zinc released during short trains of activity inhibits NMDA receptors and hence acts as an important inhibitor of hippocampal neuronal circuit excitability (Vergnano *et al.,* 2014). Zinc also acts as an inhibitory neuromodulator of glutamate release explaining its possible anticonvulsant action (Takeda *et al.,* 2004). In our study mean serum Zinc levels were significantly lower in febrile seizure children in comparison with febrile nonconvulsive children which was statistically significant. Similar resultswere replicated in studies by Karthikeyan *et al*, Salehiomran MR *et al*, Jun-Hwa Lee *et al*, Ahmad Talebian *et al*, Ganesh *et al* (Karthikeyan *et al.,* 2015; Salehiomran and Mahzari, 2013). A systematic review by Nasehi MM *et al* comparing febrile seizure group with controls concluded that low level of zinc among children can be regarded as a contributing factor for FS (Nasehi *et al.,* 2015). In study by Sreenivasa B *et al* Serum zinc level was lower in children with simple febrile seizures as compared to children with acute febrile illness and healthy children (Sreenivasa *et al.,* 2015). Low CSF Zinc levels were also observed in febrile seizure children in comparison to controls in studies by Mollah MA *et al*., 2002. However, Ihsan Kafadar *et al* in their study observed no statistically significant difference between the three groups- febrile convulsion, febrile nonconvulsive group and healthy children in terms of zinc levels. Their findings did not support the hypothesis that febrile convulsion is related to reduced serum zinc concentration, thus necessitating further studies involving larger sample sizes (Ihsan Kafadar *et al.,* 2012).

Conclusion

Our study infers that deficiency of trace elements (zinc and magnesium) may be significantly related to the risk of febrile seizures in children. Larger multicentre studies are needed to validate these results before implicating these deficiencies in pathogenesis of febrile seizures. If supported by further studies, supplementing children with the trace elements can have a good impact in preventing febrile seizures.

REFERENCES

Ahmad Talebian, Zarichehr Vakili, Safar Ali Talar, 2009. Assessment of the Relation between Serum Zinc & Magnesium Levels in Children with Febrile Convulsion. *Iranian Journal of Pathology,* 4 (4), 157 – 160.

Chhaparwal, B.C., Kohli, G., Pohowalla, J.N. *et al*. 1971. *Indian J Pediatr.,* 38: 241.

Ebel, H., Gunther, T. 1980. Magnesium metabolism: a review. *J Clin Chem Clin Biochem.,* 18: 257–270.

Fahimeh, E., Talebi-Taher, M., Vahid Harandi, N. *et al*. 2009. Serum Zinc level in children with febrile convulsion and its comparison with that of control group. *Iran J Pediatr.,* 19 (1): 65-68.

Forsgren, L., Sidenvall, R., Blomquist, H.K., Heijbel, J. 1990. A prospective incidence study of febrile convulsions. *Acta Paediatr Scand,* 79: 550-557.

Franco-Pons, N., Casanovas-Aguilar, C., Arroyo, S., Rumi, A. J., Perez-Clausell, J., Danscher, G. 2000. Zincrich synaptic boutons in human temporal cortex biopsies. *Neuroscience*, 98:429–435.

Frantzen, E., Lennox-Buchthal, M., Nygaard, A., Stene, J. 1970. A genetic study of febrile convulsions. *Neurology*, 20: 909-917.

Frederickson, C.J., Suh, S.W., Silva, D., Frederickson, C.J., Thompson, R.B. 2000. Importance of zinc in the central nervous system: the zinc-containing neuron. *J. Nutr.,* 130:1471S–1483S.

Ganesh, R., Janakiraman, L. 2008. Serum zinc levels in children with simple febrile seizures. *Clin Pediatr.,* 47:164-6.

Hauser, W.A. The prevalence and incidence of convulsive disorders in children. *Epilepsia*, 35(suppl 2): S1–6.

Ihsan Kafadar1, Ayse Burcu Akinci, Fugen Pekun, Erdal Ada, 2012. The Role of Serum Zinc Level in Febrile Convulsion Etiology. J Pediatr Inf., 6: 90-3.

ILAE, 1993. Guidelines for epidemiologic studies on epilepsy. *Epilepsia*., 34:592–6.

Iseri, L.T., French, J.H. 1984. Magnesium: nature's physiologic calcium blocker. *Am Heart J.,* 108: 188–193.

Jun-Hwa Lee, Jeong Hyun Kim, 2012. Comparison of Serum Zinc Levels Measured by Inductively Coupled Plasma Mass Spectrometry in Preschool Children with Febrile and Afebrile Seizures. *Ann Lab Med.,* 32(3):190-3.

Kaputu Kalala Malu, C., Mafuta Musalu, E., Dubru, J.M., Leroy, P., Tomat, A.M., *et al*. 2013. [Epidemiology and characteristics of febrile seizures in children]. *Rev Med Liege*., 68: 180-185.

Karthikeyan, P., Prasanna, R., Sathyamoorthy, M., Reddy, S.M., Sekar, P. 2015. Serum zinc levels in children with simple febrile seizures. *Int J Contemp Pediatr.,* 2:424-7.

Maret, Wolfgang, 2013. "Chapter 12. Zinc and Human Disease". In Astrid Sigel; Helmut Sigel; Roland K. O. Sigel. Interrelations between Essential Metal Ions and Human Diseases. *Metal Ions in Life Sciences*, 13. Springer. pp. 389–414.

Mayer, M.L., Westbrook, G.L., Guthrie P.B. 1998. Voltage-dependent block by Mg2+ of NMDA responses in spinal cord neurones. *Nature,* 309: 261–263.

Mollah, M.A., Dey, P.R., Tarafdar, S.A., Akhter, S., Ahmed, S., Hassan, T., Begum, N.A., Nahar, N. 2002. *Indian J Pediatr.,* Oct;69(10):859-61.

Nasehi, M.M., Sakhaei, R., Moosazadeh, M., Aliramzany, M. 2015. Comparison of Serum Zinc Levels among Children with Simple Febrile Seizure and Control Group: A Systematic Review. *Iranian Journal of Child Neurology.,* 9(1):17-24.

Offringa, M., Hazebroek-Kampschreur, A.A.J.M., Derksen-Lubsen, G. 1991. Prevalence of febrile seizures in Dutch school children. *Paediatr Perinat Epidemiol.,* 5:181–8.

Papierkowski, A., Mroczkowska _Juchkiewicz, A., Pawlowska _Kamieniak, A., *et al*. 1999. Magnesium and zinc levels in blood serum and cerebrospinal fluid in children with febrile convulsions. Pol Merkur Lekarski., 6(33):138-40.

Plum, Laura, Rink, Lothar, Haase, Hajo, 2010. "The Essential Toxin: Impact of Zinc on Human Health". *Int J Environ Res Public Health,* 7 (4): 1342–1365.

Salehiomran, M.R., Mahzari, M. 2013. Zinc Status in Febrile Seizure: A Case-Control Study. *Iran J Child Neurol.,* Autumn; 7(4):20-23.

Shinnar, S. 2003. Febrile Seizures and Mesial Temporal Sclerosis. *Epilepsy Curr.,* 3: 115-118.

Sreenivasa, B., Sunil Kumar, P., Manjunatha, B. 2015. Role of zinc in febrile seizures. *Int J Contemp Pediatr.,* 2(2): 137-140.

Sreenivasaiah Bharathi, Kotte Chiranjeevi, 2016. Study of serum magnesium levels and its correlation with febrile convulsions in children aged 6 months to 5 years of age. IAIM, 3(11): 61-68.

Takeda, A., Minami, A., Seki, Y., Oku, N. 2004. Differential effects of zinc on glutamatergic and GABAergic neurotransmitter systems in the hippocampus. *J. Neurosci. Res.,* 75:225–229.

Talebian, A., Vakili, Z., Talar, S.A., Kazemi, M., Mousavi, G.A. 2009. Assessment of the relation between serum zinc and magnesium levels in children with febrile convulsion. *Iranian J Pathol.,* 4(4):157-60.

Vergnano, A. M. *et al*. 2014. Zinc dynamics and action at excitatory synapses. Neuron 82, 1101–1114.

Verity, C.M., Butler, N.R., Golding, J. 1985. Febrile convulsions in a national cohort followed up from birth. II--Medical history and intellectual ability at 5 years of age. *Br Med J (Clin Res Ed),* 290: 1311-1315.

Vestergaard, M., Obel, C., Henriksen, T.B., Christensen, J., Madsen, K.M., Ostergaard, J.R. 2006. The Danish National Hospital Register is a valuable study base for epidemiologic research in febrile seizures. *J Clin Epidemiol.,* 59:61–66.

Waruiru, C., Appleton, R. 2004. Febrile seizures: an update. *Arch.Dis.Child,* 89: 751-6.

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