Research Article

Prospective Study of Level of Serum Zinc In Patients of Febrile Seizures, Idiopathic Epilepsy and CNS Infections

Lalit Kumar, Om Shankar Chaurasiya, Aditya Hari Gupta

Department of Peadiatric M.L.B. Medical College, Jhansi - 284128

Abstract:

The present study was carried out to study serum zinc levels for it's prognostic significance as well as for it's role in pathophysiology of febrile seizures, idiopathic epilepsy and acute CNS infections. In the present study, 100 cases who were admitted in our hospital during March 2009 to August 2010, aged between 1 month to 18 yrs were selected on the basis of clinical history, physical and CSF examination. They were grouped as groupA (pyogenic meningitis), group B (febrile seizures), group C (idiopathic epilepsy), group D (other acute CNS infections), group E (cerebral malaria) and group F (control). Cases of cerebral palsy, neuroanatomical malformations, neurobehavioural disorders, neurodegenerative disorders and drug induced neurological manifestations were not included in the present study. Mean serum zinc level was significantly lower in groups A, B & E, while no significant difference was observed in group C & D as compared to the control. No significant difference in serum zinc level was detected in relation to outcome and degree of consciousness in any of the study groups.

Key Words: Serum zinc, Febrile seizures, CNS infections, Idiopathic epilepsy.

Introduction:

Zinc is one of the most important trace elements that is required for proper growth and health. Being a cofactor of over 200 enzymes and a structural protein in a large number of zinc finger proteins, zinc serves a wide range of roles in human body (Frederickson,1989). Zinc is an important trace element in biology. Role of zinc in cases of acute respiratory tract infections, chronic diarrhoea and severe protein energy malnutrition has been repeatedly proved in multiple studies (Walsh et al, 1994; Halsted & Smith, 1970; Sazawal et al, 1995). But there are only very few studies on zinc status in cases of febrile seizures, septic meningitis and epilepsy (Ehsanipour et al, 2009; Garty et al, l995; Mishra et al, 2007; Prasad et al, 2009) Available data regarding role of zinc level in infections are controversial.

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 for number of different neurotransmitters. These include both excitatory and inhibiting receptors particularly NMDA (N-methyl-D-aspirate) and GABA (Gamma aminobutyric acid) receptors. This pool is 8% of total zinc content in brain.

Various workers have studied the levels of zinc in serum and cerebrospinal fluid in various CNS disorders and in normal controls. Burhanglu et al (1996) studied the role of trace elements in the pathogenesis of febrile convulsions. They studied serum Zn, Cu, Mg and cerebrospinal fluid (CSF) Zn, Cu, Mg and protein levels in patients with febrile convulsions, bacterial meningitis, viral CNS infections and in the control group. Mean serum and CSF zinc levels in the febrile convulsion group was significantly lower than in the other groups. A linear relationship was established between serum and CSF zinc level. Mean CSF zinc levels in bacterial meningitis group was significantly higher than in other groups. They suggested that in children with meningitis, the elevation of mean CSF zinc may result from breakdown of blood-brain barrier and subsequent leakage of trace elements and protein from serum to CSF. Pandey et al (1982) found the serum zinc levels to be significantly lower and CSF zinc levels to be significantly higher in patients with pyogenic meningitis as compared to controls. However, they concluded that it is not possible to predict that whether rectification of the deviant pools would benefit the patients or reduce the bioavailability of drugs administered.

There are conflicting evidences showing that at one hand zinc may act to attenuate GABA response and thereby elicit hyper excitability of neurons and induce seizure. Conversely, it has been found that zinc may act as an inhibitory neurotransmitter decreasing the likelihood of seizure (Mishra et al ,2007).

Prasad et al (2009) conducted study on CSF and serum Zn, Cu, Mg and calcium levels in children

Corresponding Author: Dr. Om Shankar Chaurasiya, Department of Pediatric, M.L.B. Medical College, Jhansi – 284128
Phone No.: +91 - 9532376316
E-mail : chaurasiyaom@gmail.com

with idiopathic seizures with normal CT/MRI and abnormal EEG. Study concluded that zinc is essential for normal development of brain. Although, CSF and serum Zn levels in patients with seizure was found to be decreased, but it was statistically insignificant. Ganesh & Lalitha (2006) evaluated serum zinc levels on 38 previously healthy children of age between 3 months to 5 years admitted with simple febrile seizure along with control. The mean serum zinc level was significantly lower in children with febrile seizures as compared to controls.

A prospective analytical case control study had been conducted by Ehsanpour et al (2009) in which ninety two children aged 6 month to 5 years were divided into three groups : group A children with febrile convulsions, group B children having fever without convulsion and group C children with non-febrile convulsion. Serum zinc level of group A was lower than those of either of two groups ($p<0.006$). Most of the above studies suggests that during acute phase of febrile convulsion there is significantly increased IL-1 (interleukin1) and PG (prostaglandin) but decreased level of serum zinc.

Aims of the present study was to evaluate the role of Zn in seizure disorders and to evaluate Zn as prognostic indicator in patients of septic meningitis, and other acute CNS infections.

Materials and Methods:

The present study was conducted on 120 patients of 1 month to 18 years of age, admitted in pediatric ward of M.L.B. Medical College, Jhansi from March 2009 to August 2010. They were divided into Group A : Pyogenic meningitis; Group B : Febrile seizures; Group C : Idiopathic epilepsy; Group D: Other acute CNS infections, including viral encephalitis, meningoencephalitis; Group E :Cerebral malaria & Group F : Control. Children of control group were those who were not manifesting any neurological disease, admitted and recovered from other illness and had not suffered in past with convulsion or any neurological disease.

Exclusion criteria: Children with cerebral palsy, metabolic disorder affecting CNS, neuroanatomical malformation, neurobehavioural disorder, neurodegenerative disorder, drug induced neurological manifestation were excluded.

Serum zinc estimation: The estimation of serum zinc was done by calorimetric test kits provided by CREST Biosystems, in the department of Pathology, M.L.B. Medical College, Jhansi. Zinc in an alkaline medium reacts with Nitro PAPS(2-[5-NITRO-2-PYRIDXY-LAZO]-5[N-nPROPYL-{3SULFOPROPYL}] AMINO PHENOL DISODIUM SALT) to form a purple coloured complex. Intensity of this complex is directly proportional to amount of zinc present in the sample. This complex absorbs light at 570 nm wavelength using yellow filter.

Taking aseptic precaution, 2ml of blood from venipuncture using 22 gauge sterile needle, was collected within 24 hours of contact of patient both from case and control groups. The sample was then centrifuged for 3-4 minutes at 3000-4000rpm; serum thus obtained was collected and preserved at 2-8°C in sterile deionised plain vials. Estimation of Zinc was carried out within 7 days of collection.

Data obtained was analyzed by GRAPHPAD SOFTWARE. A difference between two values was considered to be significant only when 'p' value was found to be <0.05. The students' test (pooled test) was used to see difference between two groups.

Results:

All the patients were divided according to age in 3 groups as: <1year, 1-5 year and > 5 years as shown in Table I.

Table I: Age wise distribution of cases in various groups:

Age group	Group A N=20	Group B N=20	Group C N=20	Group D N=20	Group E N=20	Control Group F N=20
<1	8	11	0	1	2	17
1-5	8	9	3	8	5	3
>5	9	0	12	11	13	-

The mean serum zinc level in the control (group F) was found to be 120.0±37.79 µg/dl. This value was compared with mean values of various study groups (Table II). It was observed that mean serum zinc level was significantly lower in group A, B & E as compared to control ($p<0.05$), while no significant difference was seen in group C & D as compared to control. All the patients of study group were further subdivided into conscious group & a group with altered consciousness (Table III). No significant difference in mean serum zinc level between patients of conscious group & those with altered consciousness was observed except group D. In group D serum zinc level were significantly higher ($p<0.05$) in conscious group than those of altered consciousness.

In the present study no significant difference in mean serum zinc level was observed between patient who expired and those who were discharged, left against medical advice (LAMA) or absconded (Table IV).

Table II : Serum zinc levels in various groups in relation to control.

Study groups	Mean serum zinc level ±SD (µg/dl)	Degree of freedom	t-value	p-value
Group A (pyogenic meningitis)	70.9816±59.3974l	43	3.2256	0.0024 p<0.01
Group B (Febrile seizures)	79.55±40.8445	38	3.2669	0.0023 p<0.05
Group C Idiopathic epileps	140.4±71.0342	33	1.0811	0.2875
Group D (other acute CNS infection)	125.3985±83.4871	38	0.2439	0.80806
Group E (Cerebral malaria)	90.85±48.1956	38	2.1505	0.0379 p<0.05
Group F (control group)	120.0±37.795	-	-	-

Table III : Mean serum zinc level in various study groups in relation to level of consciousness

Study groups	Mean serum zinc level ±SD (µg/dl)		p-value
	Conscious	Altered consciousness	
Group A (pyogenic meningitis)	77.666±44.134 (n=6)	69.1863±57.848 (n=19)	0.7456
Group B (Febrile seizure)	77.69±41.40 (n=16)	87.00±43.62 (n=4)	0.6947
Group C (GTCS)	179.08±62.26 (n=13)	84.00±62.23 (n=2)	0.1920
Group D (Other acute CNS infections)	220.3633±190.216 (n=3)	108.52±42.0385 (n=17)	0.0281 P<0.05
Group E (cerebral malaria)	140.00±28.28 (n=2)	85.39±43.23 (n=18)	0.1241

Table IV : Mean serum zinc level in relation to outcome.

Study groups	Mean serum zinc level ± SD(µg/dl)		p-value
	Expired	Others (discharged, lama, abscond)	
Group A (pyogenic meningitis)	46.339±7.765 (n=3)	74.6155±56.9341 (n=22)	0.407
Group B (Febrile seizure)	54.00±36.77 (n=2)	82.39±41.22 (n=18)	0.365
Group C (GTCS)	84.40±62.23 (n=2)	149.08±62.23 (n=13)	0.1920
Group D (Other acute CNS infection)	130.666±60.04 (n=3)	124.35±88.46 (n=17)	0.9077
Group E (cerebral malaria)	64.00±39.00 (n=2)	93.83±48.10 (n=18)	0.4121

Discussion

In the present study serum zinc levels in pyogenic meningitis were significantly lower as compared to control (p<0.01; Table II). This is supported by the study of Pandey et al (1982) who also found serum zinc level to be significantly lower and CSF zinc levels to be significantly higher in patients with pyogenic meningitis as compared to control. Low serum zinc levels observed in cases of pyogenic meningitis may be secondary to disease process or it may be primary hypozincemia leading to septic meningitis. The reasons are multifactorial. First, during acute phase response in infections, zinc is redistributed from plasma to the liver & to lymphocytes . This is due to liberation of endogenous mediators from polymorphonuclear leucocytes which causes a net flow of amino acids and zinc to the liver for the synthesis of acute phase reactants including metalloenzymes, thereby causing hypozincemia. This is an adaptive response intended to deprive invading pathogens of zinc. Secondly, zinc may be utilized by the organisms for growth and multiplication (Allen et al 1983; Shankar & Prasad, 1998; Sugarma et al, 1982; Vallee, 1959).

In Febrile seizure, serum zinc levels were significantly lower as compared to control (p<0.05; Table II). This observation is consistent with previous studies by Burhanglu et al (1996); Ehsanipour et al (2009) and Ganesh & Lalitha (2006). The mechanism underlying febrile convulsion, which have multiple etiologic factors, are yet not clear. Some changes in levels of proinflammatory cytokines and zinc in serum and cerebrospinal fluid have been suggested to be responsible for pathogenesis of febrile convulsion .The reason for reduction of serum zinc levels in patients affected with febrile seizure is not known. However, fever and acute infections may have some role in developing such conditions. It is believed that the release of tumour necrosis factor (TNF) and interleukin during fever or tissue injury may result in reduction of serum zinc level. Izumi et al (1990) proposed that hypozincemia trigger the NMDA receptor which is one of the members of glutamate family receptor, may play an important role in initiation of epileptic discharge.

The serum zinc concentration in idiopathic epilepsy (Group C) was found to be slightly higher than control group but the difference was not statistically significant. This result is consistent with study of Prasad et al (2009) who also found no statistically significant difference in serum zinc levels in children with idiopathic seizure as compared to control. Role of zinc in seizure is controversial as at one hand, it plays a role in synthesis and function of inhibitory neurotransmitter GABA; on the other hand it also has inhibitory effect on GABA and thus facilitating seizure activity .

The serum zinc concentration in other acute CNS infections revealed no statistically significant difference as compared to control group (p>0.05),

which is consistent with study of Burhanglu et al (1996).

The mean serum zinc concentration in study group E (cerebral malaria) was found to be lower than that of control and this difference was statistically significant ($p<0.05$). This result was consistent with the study of Duggan et al (2005) who found low plasma zinc (<9.2mmol/l) in 70% of all subjects affected with cerebral malaria.

Pandey et al (1982) reported that CSF zinc levels as compared to controls was two fold higher in pyogenic, viral and tubercular meningo-encephalitis when the patient was conscious, but are augmented by five times in the comatosed subjects.

In the present study, in group A, B, C & E there was no significant ($p>0.05$) difference in serum zinc level in relation to level of consciousness. However, patients of altered consciousness in acute viral CNS infections group (group D) showed significantly lower serum zinc levels as compared to conscious patients. Serum zinc levels were lower in expired patient of each group as compared to patient who were discharged, absconded or lama. This is supported by the fact that magnitude of change in plasma zinc is related to severity and stage of infection . Fatal outcome indicates the uncontrolled infection and more of blood brain barrier damage resulting in leakage of zinc binding metalloproteins from blood to subarachnoid spaces so low serum Zn and high CSF zinc levels. However, the difference was not statistically significant.

Zinc level was found to be significantly decreased in febrile seizures in all previous as well as in present study. Since zinc levels were also found to be significantly low in patients with septic meningitis and cerebral malaria so better response may be expected if we supplement zinc preparation while continuing other treatment in all these diseases.

Bibliography:

1. Allen J, Perri RT, McClaen CI, Kay NE: Alterations in human natural killer cell activity and monocyte cytotoxicity induced by zinc deficiency. *The Journal of Laboratory & Clinical Medicine*, 1983;102(4):577-589.
2. Burhanglu M, Tutuncuoglu S,Coker C,Tekgul H, Ozgur T Hypozincemia in febrile convulsion. *European Journal of Pediatrics*, 1996; 55(6):449-501.
3. Duggan C, William BM, Nancy FK, James LW, Walfaie WF, Zul GP, Victor M, Jonathan LS, Kojo YA, Davidson HH: Plasma Zinc concentrations are depressed in acute cerebral malaria. *The Journal of Nutrition*, 2005;135(4):802-807.
4. Ehsanipour F, Talebi-Taher, Harandi NV: Serum zinc level in febrile convulsion and its complications with that of control group. *Iran Journal of Pediatrics*, 2009;19(1):65-68.
5. Frederickson CJ: Neurobiology of zinc & zinc containing neurons. *International Review of Neurobiology*, 1989; 3l: 145-238.
6. Garty BZ, Olornucki R, Lerman - Sagie T, Nitzan M: Cerebrospinal fluid zinc concentration in febrile convulsions. *Archieves of Diseases in Childhood*, l995;73(4):338-34l.
7. Halsted JA, Smith JC: Plasma-zinc in health and disease. *Lancet* ,1970;295(7642):322-324.
8. Izumi Y, Ishii K, Akiba K, Hayashi T: Hypozincemia during fever may trigger febrile convulsion. *Medical Hypotheses*,1990;32(1):77-80
9. Mishra O P, Singhal D, Upadhyay RS, Prasad R, Atri D: Cerebrospinal fluid zinc, magnesiuim, copper and gamma-aminobutyric acid levels in febrile seizure. *Journal of Pediatrics Neurology* , 2007;5(1):39-44.
10. Pandey VK, Parmeswararn, Soman SD, Dacosta HJ: Altered sensorium in neurological infections and the homeostasis of Mg, Zinc, Cupper, Magnesium and Calcium. *The Science of the Total Environment*, 1982; 25(3):277-285.
11. Prasad R, Singh A, Das BK, Upadhayay RS, Singh TB, Misra OP: Cerebrospinal fluid and serum Zn,Cu,Mg and Ca levels in children with idiopathic seizures. *Journal of Clinical and Diagnostic Research*, 2009;3(6):1841-1846.
12. Ganesh R, Lalitha J: Serum Zinc level in children with simple febrile seizure. *Clinical Pediatrics*, 2008; 47(2);164-166
13. Sazawal S Black RE, Bhan MK, Bhandari N, Sinha A: Jalle S Zinc supplementation in young children with acute diarrhoea in India. *The New England Journal of Medicine*, 1995;333(13):839-844.
14. Shankar AH, Prasad AS: Zinc and immune function. The biological basis of altered resistance to infection. The *American Journal of Clinical Nutrition*, 1998;68(2 suppl):447S-463S.
15. Sugarmam B, Epps LR, Stenback WA: Zinc and bacterial adherence. *Infection and Immunity*, 1982;37(3):1 191-9.
16. Vallee B: Biochemistry, physiology & pathology of zinc. *Physiological Reviews*, 1959; 39(3):443-490.
17. Walsh CT, Sandstead HH, Prasad AS, Newberne PM, Fraker PJ: Zinc health effects and research priorities for the 1990's. *Environmental Health Perspectives*, 1994;102(Suppl 2):5-46.