Serum and cerebrospinal fluid zinc levels in febrile convulsions

Zübeyde GÜNDÜZ, Sefer KUMANDAŞ, İsmet YAVUZ, Mehmet KOPARAL, Recep SARAYMBN

Dept. of Pediatrics, Medical School of Erciyes University, Kayseri, TURKEY

The mechanisms underlying the febrile convulsions, which have multiple etiological factors, are not yet clear. During infectious diseases, changes in serum zinc, copper and certain plasma protein levels have been reported. In this study, we want to determine whether there are any changes in serum and cerebrospinal fluid (CSF) zinc levels of children with febrile convulsion during seizures. For this reason, 20 children with febrile convulsions, aged between 9 months and 5 years were selected as patient group and children having fever without febrile convulsions, aged between 6 months and 14 years were selected as control group; serum and CSF zinc levels were measured in both group. In the patient group, serum and CSF zinc levels were found as mean 0.698±0.095 mg/dl and mean 0.068-0.012 mg/L respectively. Whereas serum and CSF zinc levels in the control group were mean 1.054±0.066 mg/dl and mean 0.116±0.020 mg/L respectively. The zinc levels of serum and CSF samples of the patient group were significantly lower than the control group (p<0.05). [Turk J Med Res 1994, 12(6): 239-242]

Key Words: Febrile convulsion, Zinc, Cerebrospinal fluid

Febrile convulsions are brief, self-limited convulsions seen between five months and five years old normally developed children, with favorable prognosis (1,2). Role of genetic factors in its etiology is known. Several genetic trait forms are reported, however poligenic multifactorial trait is favored (3-5). The mechanisms underlying the induction of febrile convulsions are not clear. During infectious diseases, decreased serum iron and zinc, increased copper levels and changes in the concentrations of certain plasma proteins are reported (1,6). In this study, our purpose was to determine whether fever due to several causes in children between 5 months and 5 years old, cause changes in serum Zn levels; if there, are any, these changes have an effect in the pathogenesis of febrile convulsions or not?

MATERIALS AND METHODS

The study was carried out in Erciyes University Faculty of Medicine Pediatrics Department. A patient group of 20 children; 6 girls (30%), 14 boys (70%) between 9 months and 5 years old (mean age 25.1±17.0 months), who visited the Pediatric Emergency Department of our faculty with febrile convulsion complaints; total 10 pediatric control group of 5 girls (50%) and 5 boys (50%) between 6 months and 4 years old (mean age 25.0±16.0 months) who visited for fever and examined for etiology but did not have convulsion (Table 1)-

Children in our study had physical examination and evaluated for development, blood haemoglobin, white blood cell counts were measured, peripheral blood smears were evaluated, urine samples were tested, chest X-rays were taken and blood and urine cultures were done.

Serum Na^{+}, K^{+}, Cl^{-}, Ca^{++}, phosphorus, alkaline phosphatase, blood glucose values and two directional cranial X-rays were normal in both groups. There is no cell in CSF samples taken by lumbar puncture. CSF protein and glucose levels were in normal limits. Fever was due to respiratory and urinary tract infections in all patients.

As shown in Table 2, in patient group serum and CSF Zn levels were 0.54-0.84 mg/dl (mean 0.698+0.095) and 0.04-0.09 mg/L (mean 0.068±0.012) respectively. In control group serum and CSF Zn levels were 0.95-1.17 mg/dl (mean 1.054±0.066) and

Received: April 3, 1993 **Accepted:** Oct. 10,1994

Correspondence: Zübeyde GÜNDÜZ
Dept. of Pediatrics
Medical School of Erciyes University,
Kayseri, TURKEY

Table 1. Age and sex distribution of groups

		The patient group	The control group
Sex	Female	6	5
	Male	14	5
Age		9 months to 5 years mean 25.05±16.09 months	6 months to 4 years mean 25.10±15.85 months

0.08-0.14 mg/L (mean 0.116±0.020) respectively. In patient group serum and CSF Zn levels were lower than control group ($p<0.05$).

Thirteen patients had one and 7 patients had more thar one convulsions. We couldn't find any difference between serum and CSF Zn levels in patients with one and in patients with more than one convulsions ($p>0.05$). Serum and CSF Zn levels in patients with one convulsion and in patients with more than one convulsions are shown in Table 3.

DISCUSSION

In etiology of febrile convulsions, in addition to genetic factors, also maternal disease, maternal smoking, abnormal pregnancy and birth history take roles as predisposing factors (10,11). Although its occurence mechanisms are controversial, febrile convulsions are generally thought to be induced by metabolic changes during the rising-phase of body temperature (1). On the other hand, as a trace element, Zn is necessary component of more than 200 metalloenzymes including some enzymes which play an important role in the central nervous system (CNS) (1,12). Zn deficiency may cause malformations and malfunction of the CNS in the fetus (1,12,13). It is present in high concentrations in the cortex, especially in the mossy fiber axons of the hippocampal dentate gyrus granule neurons (1,14-16). Zinc, localized in the mossy fiber terminals may play a role in the neurotransmitter regulation on the hippocampus. Some evidence suggests that the zinc pool associated with the mossy fiber terminals may be released by nerve stimulation (14,15,17). These findings may indicate that zinc may be associated with the etiology and manifestations of epileptic seizures.

In animals, intracerebroventricular injection of zinc has been shown to cause epileptic seizures, but this effect has been postulated because of direct application of relatively high concentrations of zinc In the CNS (1,15).

In literature, there are some studies which suggest that zinc in the physiological concentrations decrease the convulsions. Fukohori et al (15) demonstrated that zinc concentrations are very low in the hippocampal dentate area of genetically epileptic mouse. In this study, it has been noted that the seizure suspectibility of the epileptic mouse was increased by zinc deficiency, and decreased by zinc loading.

The changes in CSF Zn levels were determined in some neurological diseases. In Guillian-Barre Syndrome, malign brain tumors, subarachnoid haemorrhage, and acute cerebrovascular diseases, CSF Zn levels have been found elevated (12,18). In epileptic patients, serum zinc levels are reported normal (19) or decreased (1). Goldberg et al (20) also found decreased CSF zinc levels of babies with fifth days fits, and concluded that convulsions may due to temporary zinc deficiency.

Infectious diseases cause nonspesific host responses such as neutrophilic leukocytosis, hypoferramia, hypozincemia, hypercupremia and changes in the concentrations of certain plasma proteins in addition to fever (1,6). It is generally believed that fever is mediated by endogenous pyrogen proteins which are produced by leukocytes and other phagocytic cells and act on CNS temperature regulating centres. Leukocytic endogenous mediator which is an endogenous pyrogen protein and released by phagocytic cells, causes decrease in the plasma concentrations of zinc and iron during both infection and endotoxinemia (6).

Table 2. Comparison of serum and CSF zinc levels in patient and control group

Test	The patient group n	X±Sx	The control group n	X±Sx	P
Serum zinc	20	0.698±0.095 mg/dl	10	1.054±0.066 mg/dl	<0.05
CSF zinc	20	0.068±0.012 mg/L	10	0.116±0.020 mg/L	<0.05

Table 3. Comparison of serum and CSF zinc levels between patients with one convulsion and more than one

Test	Patients with one convulsion n	X±Sx	Patients with more than one convulsion n	X±Sx	P
Serum zinc	13	0.723+0.097 mg/dl	7	0.687+0.090 mg/dl	>0.05
CSF zinc	13	0.068+0.014 mg/L	7	0.069+0.011 mg/L	>0.05

Van Miert et al (6) demonstrated that plasma zinc and iron concentrations decrease during some infectious diseases, but no clear relationship was found between the temperature responses and the alterations in plasma trace metal concentrations. However the mechanism of the decrease in extracellulary fluid zinc levels during infectious diseases is unclear.

The mechanusms by which depletion of zinc facilitates epileptogenic activity is unclear. Khulusi et al (16) demonstrated that evoked potentials in mossy fibers decreased with zinc addition. There is some evidence that zinc regulate the evoked and inhibitory synaptic transmission in the hippocampus (21). It has been reported that zinc decrease the evoked potentials by increasing the effects of gamma-aminobutyric acid (GABA) and blocking the N-methyl-D-aspartate (NMDA) receptors (1,16,21,22).

In the pathophysiology of febrile convulsions, we thought that extracellulary fluid zinc decreased by several mechanisms during acute infections may also be effective in addition to fever which have an effect on neuronal susceptibility. The reduction of extracellulary zinc levels in the CNS caused by hypozincemia facilitates neuronal susceptibility through a mechanism that activates the NMDA receptor and/or the disinhibition of GABAergic action and results by febrile convulsions. For this reason we planned to study serum and CSF zinc concentrations in patients with febrile convulsions.

In our patients serum and CSF zinc levels were lower than control group ($p<0.05$) (Table 2). Results of our study showed that seizure numbers are unrelated to serum and CSF zinc levels. In Guciiyener's study (23) in contrast to our results, CSF zinc levels in children with febrile convulsions are similar to control group. Different results in these two studies thought that further studies in larger groups are necessary.

Febril konvülzyonlarda serum ve beyin omurilik sıvısı çinko düzeyleri

Etyolojisinde değişik faktörlerin rol oynadığı tf 'il konvulziyonların oluş mekanizmaları tam olarak aydınlatılamamıştır. İnfeksiyon /ustalıkları esnasında serum çinko, demir, bakır vt bazı plazma proteinlerinde değişikliklerin olduğu bildirilmektedir. Bu çalışmada febril konvulziyonlu çocukların konvulziyon sırasında serum ve beyin omurilik sıvısı (BOS) çinko düzeylerinde değişiklik olup olmadığı araştırıldı. Bu amaçla yaşları 9 ay-5 yaş arasında olan ve febril konvulziyon geçiren 20 çocuk hasta grubu olarak, yaşları 6 ay-4 yaş arasında ateşi olan fakat konvulziyon geçirmeyen 10 çocuk kontrol grubu olarak alındı.

Hasta grubunun serum ve BOS çinko düzeyleri sırasıyla ort. 0.698+0.095 mg/dl ve ort. 0.068+0.012 mg/L olarak bulundu. Kontrol grubunun serum ve BOS çinko düzeyleri ise sırasıyla ort. 1.054+0.066 mg/dl ve ort. 0.116+0.020 mg/L idi. Hasta grubunun serum ve BOS çinko düzeyleri kontrol grubunun düzeylerinden düşüktü ($p<0.05$). [TurkJMedRes 1994, 12(6): 239-242]

REFERENCES

1. Izumi Y, Ishü K, Akiba K et al. Hypozincemia during fever may trigger febrile convulsion. Medical Hypothesis 1990; 32:77-80.
2. Nelson KB, Hirtz DG. Febrile seizures. In: Swaiman KF, ed. Pediatric Neurology. Principles and Practice. St Louis: The CV Mosby Company, 1989:439-42.
3. Brett EM. Epilepsy and convulsions. In: Brett EM, ed. Pediatric Neurology. Edinburgh: Churchill, Livingstone, 1991:317-88.
4. Deger R, Degen HE, Hans K. A Contribution to the genetics of febrile seizures waking and sleep EEG in siblings. Epilepsia 1991; 32(4):515-22.
5. Tsuboi T. Genetic aspects of febrile convulsions. Hum Genet 1977; 36:169-73.
6. Van Miert A, Van Duin C, Verheijden J et al. Fever and changes in plasma zinc and iron concentrations in the goat: The role of leukocytic pyrogen. J Comp Path 1984; 94:543-57.
7. Tietze NW. Textbook of Clinical Chemistry. WB Saunders Company, 1986:287-458, 619-763, 695-996, 1495-588.
8. Palm R, Sjöström R, Hallmans G. Optimized atomic absorption spectrophotometry of zinc in cerebrospinal fluid. Clin Chem1983; 29(3):486-91.
9. Sümbüloglu K, Sümbüloglu V. Biyoistatistik. Ankara: HatipogluYayinevi, 1990:114.
10. Nelson KB, Ellenberg JH. Prenatal and perinatal antecedents of febrile seizures. Ann Neurol 1990; 27:127-31.
11. Wallace SJ. Aetiological aspects of febrile convulsions. Pregnancy and perinatal factors. Arch Dis Child 1972; 47:171-8.
12. Palm R, Hallmans G. Zinc concentrations in thé cerebrospinal fluid of normal adults and patients with neurological diseases. J Neurol Neurosurg Psychiatry 1987; 45:685-90.
13. Standstead HH. Zinc: Essentiality for brain development and function. Nutrition Reviews 1985; 43(5):129-37.
14. Assay SY, Chung SH. Release of endogenous Zn^{2+} from brain tissue during activity. Nature 1984; 308:234-6.
15. Fukahorl M, Itoh M. Effects of dietary zinc status on seizure susceptibility and hippocampal zinc content in the EL (epilepsy) mouse. Brain Research 1990; 529:16-22.
16. Khulusi SS, Brown MW, Wright DM. Zinc and paired-pulse potentiation in the hippocampus. Brain Research 1986; 363:152-5.

17. Howell GA, Welch MG, Frederickson CJ. Stimulation-induced uptake and release of zinc in hippocampal slices. Nature 1984; 308:236-7.

18. Sarıalp A. Akut serebrovasküler hastalıklarda serum ve BOS bakır, çinko ve magnezyum düzeyleri ve BBT bulgularıyla ilişkisi. Uzmanlık Tezi. Kayseri, 1991.

19. Özel A. Epilepsili çocuklarda serum bakır, çinko düzeyleri ve antiepileptik ilaçların etkisi. Uzmanlık Tezi. Kayseri, 1984.

20. Goldberg HJ, Sheehy EM. Fifth day fits: an acute zinc deficiency syndrome? Arch Dls Child 1982; 57:633-5.

21. Westbrook GL, Mayer ML. Micromolar concentrations of Zn^{2+} antagonize NMDA and GABA responses of hippocampal neurons. Nature 1987; 328:640-3.

22. Peters S, Koh J, Choi DW. Zinc selectively blocks the action of N-Methyl-D-Aspartate on cortical neurons. Science 1987; 263:589-93.

23. Gücüyener K. Excitatory amino acids and N-methyl-D-aspartate receptor in patients with febrile convulsions. European Federation of Child Neurology Society (ESCNS) meeting of Berne. Switzerland, 1993:24-6.