Correspondence

Serum levels of zinc and copper in epileptic children during long-term therapy with anticonvulsants

To the Editor

We have read with interest the study by Talat et al on the serum levels of zinc (Zn) and copper in epileptic children during long-term therapy with anticonvulsants. It is obvious that there is a mutual correlation between nutrition and neurological disorders. On one hand, clinical manifestations accompanying neurological diseases are generally diverse and affect multiple organs. Nutritional status of patients with certain neurological diseases, including epilepsy, can be altered because of symptoms associated with disease course, including certain micronutrient deficiency [folic acid, Zn, vitamin B6 and B12, vitamin D, vitamin E, and vitamin C], changes in energy expenditure, intake decreased, gastrointestinal disorders, and dysfunction of the bone mass. Also, other factors ought to be considered in account like advanced age, multiple co-morbidities, polypharmacy, the use of herbal products, social habits, diet, and pharmacological treatments effect. On the other hand, certain micronutrients like Zn is crucial for neuronal signaling and synaptic function. Alterations in brain Zn status have been implicated in a wide range of neurological disorders, including impaired brain development and many neurodegenerative disorders such as Alzheimer’s disease, and mood disorders including depression, Parkinson’s disease, Huntington’s disease, amyotrophic lateral sclerosis, and prion disease. Furthermore, Zn also has been implicated in neuronal damage associated with traumatic brain injury, stroke, and seizure. Understanding the mechanisms that control brain Zn homeostasis is thus critical to the development of preventive and treatment strategies for these and other neurological disorders.

Talat et al demonstrated in their study that the mean serum Zn levels in epileptic children under long-term therapy with anticonvulsants (60.1±22.6 ug/dl) were significantly lower compared with healthy children (102.1±18 ug/dl) (p<0.001). Accordingly, the authors recommended measuring serum Zn level in epileptic patients on long-term anticonvulsant therapy and to give them Zn supplements if proved to be Zn deficient. Despite the limitations addressed by Talat et al in their study, we do agree with their recommendation and I support it with the following 4 points. 1.) Studies employing animal models have shown that Zn treatment had proconvulsant activity and increased blood-brain barrier permeability, possibly changing prooxidant/antioxidant balance and neuronal excitability during seizures. Moreover, Zn supplementation was unlikely to have any undesirable effect when used in epileptics rather it may offer advantage in epileptic and seizure prone patients. 2.) Though rarely reported in the literature, the potential proconvulsant effects of oral Zn supplementation in an epileptic patient has been addressed. 3.) There is a growing body of evidence on the promising efficacy of oral Zn supplementation in children with intractable epilepsy (IE). In a recently published Egyptian study, children diagnosed with idiopathic IE were randomly allocated to 2 groups: the intervention group received oral Zn supplementation (1 mg/kg/day) while the placebo group received placebo, each for 6 months. Supplementation with Zn resulted in a significant reduction of seizure frequency in 31% of the treated children. 4.) The burden of epilepsy is devastating and includes social and medical morbidity of the disorder and where epileptic patients are greatly stigmatized and frequently untreated, particularly in developing countries. Epilepsy adversely affects childhood development and could lead to increased economic burden in pediatric populations. Hence, the inclusion of Zn supplements into the treatment regimen of pediatric epilepsy is solicited to be economically profitable because it allows to improve the quality of life of epileptic children, minimizes the costs of frequent hospital visits and recurrent hospitalizations, and maintains foreseeable manpower resources.

Finally, we presume that there is a need to conduct a large scale randomized prospective clinical trial in order to investigate the effect of combing oral Zn supplementation with antiepileptic drugs for treating epilepsy in children in terms of the optimum Zn therapy regimen and the frequency of seizures.

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Reply from the Author

The role of Zn in seizure is controversial as at one hand, it plays a role in the synthesis and function of inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and on the other hand, it also has an inhibitory effect on GABA and thus facilitating seizure activity. Many studies were carried out to clear that role but the majority were observational (assessment Zinc level in epileptic patients) and few studies were interventional.
or therapeutic. As regards Prof. Al-Mendalawi’s correspondence, he reported that studies employing animal models have shown that Zn treatment had proconvulsant activity and increased blood-brain barrier permeability, possibly changing prooxidant/antioxidant balance and neuronal excitability during seizures.\(^4\)

We believe that the first evidence is not an appropriate for Zn supplement in epileptic patient as the study found that Zn supplementation for 2 months did not show a protective effect on increased blood-brain barrier (BBB) permeability during convulsions. Moreover, there were no changes in severity and duration of seizure intensity and arterial blood pressure between animals treated and untreated with Zn. They also found that Zn by itself caused BBB breakdown without seizures and they believe that Zn might cause an imbalance between ionic homeostasis in the brain. Significant increases of Zn amount in all brain regions under study were observed in all groups compared with the control group. According to this result, Zn accumulation may provoke BBB breakdown during epileptic seizures. Zn is a potent Na-K-ATPase inhibitor like Barbeau et al\(^{10}\) who showed that intracerebroventricular Zn inhibited Na-K-ATPase and resulted in convulsions by increasing cerebrospinal fluid potassium levels.\(^{10}\) So, Zn treatment had proconvulsant activity not anticonvulsant activity.

Surely, we agree that there is a need to conduct a large scale randomized prospective clinical trial more than that carried out by Saad et al\(^7\) study which include only 45 children diagnosed with idiopathic intractable epilepsy at Assiut University Hospital, Assiut, Egypt to investigate the effect of combining oral Zn supplementation with antiepileptic drugs for treating epilepsy in children in terms of the optimum Zn therapy regimen and the frequency of seizures.

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