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Association of Serum Zinc Level with Severe Pneumonia in Children

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Abstract: Pneumonia is the leading cause of childhood mortality especially in developing countries affecting approximately 151 million cases each year. Malnutrition especially deficiency of micronutrients such as zinc, has shown to increased incidence and severity of pneumonia. In developing countries zinc deficiency is common in children due to lack of intake of animal foods and high dietary phytates (myoinositol hexaphosphate) content. This study was designed to document the association of serum zinc level with severe pneumonia in children of 2-60 months age. A case-control study was conducted in the department of physiology, Liaquat University of Medical and Health Sciences, Jamshoro and cases were collected from outpatient department of pediatrics, Liaquat Medical College and Hospital Jamshoro, Sindh-Pakistan. Fifty cases of severe pneumonia and fifty cases of control group of same age, sex and nutritional status were recruited for the study. Mean±SD serum zinc level of group I was 184.92±44.11 µg/dl and it was 206.76±47.59 µg /dl for group II, which was highly significant statistically (p = 0.019).

Key words: Pneumonia, serum zinc, nutritional status

INTRODUCTION

Worldwide, pneumonia is the leading cause of pediatric morbidity and mortality. It is estimated that pneumonia is responsible for more than two million deaths each year in children less than five years age, which represents 19% of the annual deaths in this age group (Igor Rudan *et al.*, 2008; Bhatnagar and Natchu, 2004). In low-income countries, under-nutrition is associated with a greater severity of pneumonia, a longer duration of illness and an increased case fatality rate (Michael Hambidge, 2006; Ugwuja *et al.*, 2007). Approximately 95% of the pneumonia-related deaths occur in developing countries and the youngest age group have the highest risk of death (Kumar *et al.*, 2004). Of the micronutrients, zinc plays a critical role in the development and maintenance of host defenses against infectious diseases (Ken Brown *et al.*, 2003; Peter Va, 2006). Mild to moderate zinc deficiency is common in several developing countries because the commonly consumed staple foods have low zinc contents and are rich in phytates, which inhibit the absorption and utilization of zinc (Shankar and Prasad, 1998). Zinc deficiency results in impaired immunity, which may increase the risk of infections (Prasad *et al.*, 1963).

Conflicting observations have been reported regarding the role of zinc against acute lower respiratory tract infection (Shankar and Prasad, 1998; King *et al.*, 2000). Our study would be first of its kind in Pakistan, showing the relationship of lower serum zinc and pneumonia.

MATERIALS AND METHODS

A case-control study was conducted at Liaquat University Hospital Jamshoro, Sindh-Pakistan, which is a tertiary health care provider and teaching facility covering almost the entire Sindh province except Karachi. Children of 2-60 months age presented with severe pneumonia at Out Patient Department (OPD) from May 2008 to December 2008 were conveniently paired with healthy controls for age, sex and nutritional status. A well informed consent was obtained from the guardians/care giver of every subject. Severe pneumonia was diagnosed according to the World Health Organization (WHO) case definition. Children with clinical diagnosis of associated diseases like diarrhea, allergic disease, asthma, chronic cough, documented tuberculosis or taking zinc supplementation were excluded from the study. Detailed information was obtained regarding anthropometry of the subjects.

Patients were examined clinically and according to WHO case definition of severe pneumonia they were looked for subcostal, intercostals and sub-sternal chest in-drawing and according to weight for age they were classified in different nutritional groups as Normal (at 80% or above weight for age) Grade I (70-79% weight for age) and Grade II (60-69% weight for age).

From all participants blood was drawn from any visible prominent veins, in cubital fosse and/or hands. The site cleaned with antiseptic solution and 2 ml of blood was drawn by syringe or by butterfly. Blood was collected in BD vacutainer tube.

After labeling the samples were sent to diagnostic laboratory at Liaquat University Hospital, Hyderabad where serum was obtained by spinning at 3000 rpm for 10 min and sample were stored at -20°C. After collection of required number of samples, they were sent to Pakistan Council of Scientific and Industrial Research

Laboratory (PCSIR) Karachi for analysis of serum zinc by graphite atomic absorption. The standard method of serum analysis by graphite atomic absorption was adopted. Hitachi Z-8000 Atomic Absorption Spectrophotometer (Tokyo, Japan) graphite furnace (GFAAS) with deuterium background correction equipped was used. The hollow cathode lamp of Zn was run under the conditions suggested by the manufacturer.

Digestion of samples was carried by microwave procedure. Duplicate samples of 0.5 ml of serum were directly placed into Teflon PFA flasks. One milliliter of a freshly prepared mixture of concentrated HNO_3-H_2O_2 (2:1, v/v) were added to each flask and placed in a covered poly (tetra-fluoroethene) container, heated following a one-stage digestion program at 80% of total power (900 W) for 2 min for serum. After the digestion, the flasks were left to cool and diluted to 10.0 ml in volumetric flasks with deionized water.

A Pel (PMO 23) domestic microwave oven (900 W maximum heating powers) was used for the digestion of the samples. Centrifugation was carried out to separate the supernatant from the sample extracts with a WIROWKA Laboratoryjna type WE-1, nr-6933 centrifuge, with speed range 0-6,000 rpm.

The data were collected on a predesigned proforma. Variables analyzed were age, sex and nutritional status. Statistical analysis was performed through SPSS version 14.0 for windows. Means with standard deviations were calculated for quantitative data and their P-values were obtained by applying Student's t-test. Chi square test was applied to analyze categorical data.

RESULTS

Fifty consecutive cases of severe pneumonia 2-60 months of age were paired conveniently for age, sex and nutritional status with healthy controls during the study period. There were 35 (70%) males and 15 (30%) females in each group. Mean±SD age of each group was 30.46±18.9 months. Fifteen (30%) subjects in each group were of 2-12 months of age and 35 (70%) were of 13-60 months of age. Nutritional status of 12 (24%) subjects was normal, 14 (28%) were of grade I and 24 (48%) were of grade II in each group. Mean±SD weight of cases was 9.55±3.307 kg and it was 10.9±3.312 kg in controls (p = 0.415). These baseline characteristics are detailed in Table 1. Mean±SD serum zinc level in cases was 184.92±44.11 µg/dL and in controls it was 206.76±47.59 µg/dL (p = 0.019). The association of serum zinc level in both groups is detailed in Table 2.

Table 1: Baseline characteristics of both groups

	Cases (n = 50)	Controls (n = 50)
Sex		
Males	35 (70%)	35 (70%)
Females	15 (30%)	15 (30%)
Age		
2-12 months	15 (30%)	15 (30%)
13-60 months	35 (70%)	35 (70%)
Nutritional status		
Normal	12 (24%)	12 (24%)
Grade I	14 (28%)	14 (28%)
Grade II	24 (48%)	24 (48%)

DISCUSSION

Current well-designed randomized controlled trials of zinc supplement in young children shows decrease morbidity and mortality in infectious diseases has highlighted zinc deficiency as a public health problem of global proportion (Jones *et al*., 2003). Next to diarrhea, pneumonia is the most prevalent cause worldwide of infectious disease mortality in young children.

The most extensive and impressive data related to the use of zinc as a preventive modality with lower mortality, significantly due to pneumonia is available. But the results of zinc administered as adjuvant therapy for pneumonia have been more limited. In a recent study in Bangladesh, zinc given together with antimicrobial therapy to young children suffering from pneumonia was associated with a significant reduction in the duration of pneumonia compared with that in the control group, who received the same antimicrobial therapy without Zinc supplements (Brooks *et al*., 2005).

A pharmacological effect of zinc is plausible but it is widely accepted that the beneficial effects of zinc supplements in the prevention and treatment of acute pneumonia are most likely to be due to the prevention or correction of zinc deficiency. Hence, beneficial effects of zinc supplements in the acute management of

Table 2: Associations of serum zinc level with different parameters

	Cases (n = 50)	Controls (n = 50)	p-value
Serum zinc level (mean±SD)	184.92±44.11 µg/dL	206.76±47.59 µg/dL	0.019
Age			
Up to 1 year	196.93±22.32 µg/dl	223.4±50.57 µg/dl	0.004
>1 year	179.77±50.07 µg/dl	199.63±45.13 µg/dl	
Sex			
Males	187.29±47 µg/dl	214.17±51.59 µg/dl	0.09
Females	179.4±37.39 µg/dl	187.71±28.8 µg/dl	
Nutritional status			
Normal	206.17±49.69 µg/dl	251.43±47.01 µg/dl	<0.001
Grade I	203.36±33.48 µg/dl	207.46±27.95 µg/dl	
Grade II	163.54±37.55 µg/dl	179.17±35.31 µg/dl	

pneumonia are not to be expected unless the infant or child is Zinc deficient.

Dietary zinc requirement varies with age in young children. Prolong breast feeding and consumption of complementary food which is plant based doesn't fulfill zinc requirement of children in developing countries. Infants delivered at term and who are appropriate for gestational age have sufficient zinc intakes for the first 4 months of life but as they grow older zinc requirements are increased and plant based weaning diet do not provide adequate zinc. So typically infants more than 6 months of age in developing countries will fail to meet zinc requirements. And suggestion of zinc supplements for the treatment of pneumonia is more likely to be effective in this age group (Michael Hambidge, 2006).

Possibly the effect of zinc is on the extent of inflammation and its resolution rate surrounding infection. Zinc supplementation might protect the lung from inflammatory states, whereas zinc deficiency might enhance airway inflammation and cellular damage. In the presence of zinc, there is decreased inflammation of other organ systems and increased bacterial inhibition and cellular regeneration. Thus, zinc may reduce inflammation and lower airway obstruction, in supplemented children and contribute to faster inflammation resolution time, manifested by shorter duration of chest in-drawing, high respiratory rate and hypoxia (Brooks *et al*., 2004).

This study was designed to determine the serum zinc levels in children suffering from pneumonia compared to age, sex and nutrition status.

The results of this study revealed that serum zinc level has no significant correlation with sex.

Similar observations were reported by Shakur MS and associates (Shakur *et al*., 2004). Strand RA and colleagues also reported the no significant difference in serum zinc level between both sexes in their study (Tor Strand and Maria Mathisen, 2005). Our study serum zinc level was raised in children of 2-12 months of age ($p = 0.004$) and is similar to that reported by other studies (Bahl *et al*., 1998).

The mean±SD weight of studied population was 10.59±3.16 kg, which is almost same as observed by Ugwuja et al in their study (Ugwuja *et al*., 2007).

In this study it was found that serum zinc level of cases, when compared to age, sex and nutritional status matched controls, were found to be significantly low. One explanation for lower zinc level in severe pneumonia can be pre-existing deficiency making the child susceptible to pneumonia due to impaired immunity. In addition, respiratory tract infections are also known to result in lower zinc levels in response of cytokines (IL-6) which causes shifting of zinc from plasma to liver. That was also observed in previous studies in which serum zinc level was significantly higher at the discharge than at baseline which shows cessation of acute phase response. It was observed in present study that low serum zinc levels were present even in well nourished children suffering from severe pneumonia as compared to controls. The association between nutritional status and serum zinc levels was directly proportional to each other ($p = 0.004$).

Although the present findings are promising, but there is currently no standard guidelines to use Zinc in all malnourished children to prevent pneumonia and additional studies are needed to further investigate whether Zinc should be given to all malnourished children as standard of care and if there are any other micronutrients also play a role as sole deficiency or along with Zinc to boost immunity and any other environmental risk factor or co-morbidities put the kids at the risk of pneumonia and what is the relationship of Zinc level in children with or without pneumonia in developed countries.

Conclusion: Children suffering from severe pneumonia have decreased level of serum zinc as compared to healthy controls.

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