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Serum zinc levels as a predictor of clinical features and outcome of paediatric acute lower respiratory infections in Nigeria

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Abstract Background: Malnutrition, especially macronutrient deficiency, has been shown to be interrelated with ALRI-related morbidity and mortality. However the import of zinc deficiency has only recently become the focus of research attention.

Objective: The current study was carried out in Ilorin, Kwara State, Nigeria to determine the relationship between serum zinc levels, clinical features and outcome in hospitalized children with acute lower respiratory infections (ALRI).

Method: A descriptive cross-sectional hospital-based study involving 120 children aged two months to five years with ALRI. Socio-demographic, clinical and laboratory data were obtained. The serum zinc was analyzed with a Jenway™ spectrophotometer after initial preparation with the QuantiChrom™ zinc assay kit.

Results: Children with tachypnoea and crepitations had significantly lower mean serum zinc levels compared to the corresponding values in those without these fea-

tures (each $p < 0.05$). Significantly higher mean serum zinc level was recorded in children with grunting respiration compared with those without grunting ($p = 0.028$). Age-related tachypnoea, grunting, and crepitations remained significant (each $p < 0.05$) following a linear regression analysis. The mean serum zinc level in children with multiple complications was significantly lower than the corresponding level recorded in children who had one complication, $p = 0.020$. No significant difference was found between the mean serum zinc level of the children who were discharged compared with the corresponding level recorded in those that died, $p = 0.589$.

Conclusion: The presence of crepitations had the strongest clinical association with a low serum zinc level. Children managed for ALRI would benefit from post-treatment zinc supplements and appropriate zinc-rich sources of food at discharge.

Keywords: Children zinc respiratory infections

Introduction

Malnutrition and acute lower respiratory infections (ALRI) are inter-related paediatric morbidities, especially in the developing world. A recent WHO report estimates that 6.9 million children under five years of age died in 2011.¹ About 80 percent of the world's under-five deaths in 2011 occurred in only 25 countries, and about half in only five countries including Nigeria, which together account for more than a third of under-five deaths worldwide.¹ Globally, pneumonia is one of the four major killers of children under age five years. Whereas macronutrient deficiency has continued to attract significant research interest, the import of zinc

and other micronutrients has only recently become the focus of research attention. Zinc is a trace element which stimulates the activity of multiple enzymes involved in various metabolic and immunologic responses in the body.² This element is known to have a direct anti-viral activity and a demonstrable effect on immune-mediated production of interferon.^{3,4} Also, zinc prevents pathogens from gaining entry into cells and hinders their intra-cellular multiplication.^{3,4} Zinc deficiency not only decreases the ability of the body to respond to infection, but also adversely affects both cell-mediated and humoral immune responses.³ The current study was carried out in Ilorin, Kwara State in the North Central region of Nigeria to determine the relationship between the serum

zinc levels and clinical features in hospitalized children with ALRI syndromes of bronchiolitis and pneumonia as well as the outcome of the illness.

Materials and Method

This descriptive cross-sectional study was conducted in the Emergency Paediatric Unit (EPU) and the Paediatric Medical Ward of the University of Ilorin Teaching Hospital (UIITH), located in Ilorin South Local Government Area (LGA) of Kwara State. Ilorin is the capital city of Kwara State, situated in the North Central geopolitical zone of Nigeria.

Using the Fisher's formula⁵ and a prevalence of 15.8 % from a previous study,⁶ the minimum sample size of 102 was calculated but 120 subjects were recruited for ease of analysis. Children aged between two months and up to five years with an admission diagnosis of ALRI (either pneumonia or bronchiolitis) were recruited and followed up until discharge consecutively over a four month period (April-July, 2010).

Inclusion criteria included those with a diagnosis of pneumonia based on the presence of acute cough, fever, breathlessness, age-related tachypnoea and auscultatory findings of one or more of reduced breath sound intensity, bronchial breath sounds and crepitations.⁷ This was corroborated with the presence of patchy opacities in one or more lobes, or lobar/ segmental consolidation with or without the air bronchogram sign. Bronchiolitis was diagnosed based on the presence of cough, fever, wheezing and dyspnoea, associated with bilateral polyphonic expiratory rhonchi, inspiratory crepitations and clinical/radiographic features of hyperinflation.⁷

Exclusion criteria included children who had: received any form of zinc supplementation in the preceding one month, the severe forms of PEM (marasmus, kwashiorkor and marasmic-kwashiorkor), sickle cell disease, diarrhoea in the preceding one month, previously been recruited for the study and representing with symptom recrudescence.

Ethical approval was obtained from the ethical committee of the hospital. A semi-structured questionnaire was administered to obtain the clinical data from the caregiver after obtaining an informed consent.

Questions were asked on the presence/absence of specific symptoms such as cough, fever, inability to feed or drink, rapid or difficult breathing. The respiratory rate was counted by observing each upward movement of the abdominal/chest wall for one minute. Tachypnoea was present if the respiratory rate was >50 breaths/min for infants aged two months up to one year, and > 40 breaths/min for children aged 12-59 months. Chest wall indrawing was identified as inward movement of the lower chest wall on breathing in with the child lying flat on either the caregiver's lap, or the examination table

after adequate exposure. The presence of various clinical signs such as nasal flaring, grunting, wheeze, and central cyanosis were documented. Findings on percussion over the intercostal spaces in the anterior and posterior chest wall were recorded as normal, dull or hyper-resonant. Auscultatory signs like the presence of diminished intensity of breath sounds, crepitations, bronchial breath sounds, and rhonchi were recorded. Other relevant physical examination included identifying the presence/absence of oedema, and skin changes such as peeling/hypopigmentation around the perineum and acro-orificial areas. Chest radiographs were obtained in all subjects.

Using strict aseptic techniques, two millilitres (mls) of blood was collected via venepuncture, aliquoted into a plain bottle, and allowed to clot. Serum samples were obtained by centrifuging the clotted blood sample at 3000rpm for five minutes in a bench-top centrifuge. The sera obtained were transferred into sterile plastic tubes and stored immediately at -20°C, till it was ready to be analyzed when the sera were thawed followed by batch analysis. Unhaemolyzed sera were used, and any serum which was neither clear nor colourless was discarded

The serum zinc analysis was done with a Jenway™ spectrophotometer 6300 model (*Jenway Limited, Dunmow, Essex, United Kingdom*) for measuring optical density at 425nm, after an earlier preparation with the QuantiChrom™ Zinc colorimetric assay kit (*Bioassay Systems, Hayward, California, USA*).⁸ The Zn²⁺ Standard (10µM), 50µl of water, Sample and Sample Blank (50µL sample + 2µL EDTA) were transferred into wells of a clear bottom 96-well plate.⁸ Subsequently 200µL of the working reagent was added to each well and then mixed by tapping the plate lightly. The resulting solution was allowed to incubate for 30 minutes at room temperature.⁸ The optical density (OD) was read at 420-426nm (peak absorbance at 425 nm).⁸ For this study, a value of 57µg/dl was used as the lower cut-off for low serum zinc concentrations.⁹

Data was analysed using the SPSS 16 software package. Frequencies, proportion, means and standard deviations were calculated. The *Student's t-test* was used to identify significant differences for continuous variables. A linear regression analysis was also done among the continuous variables that were significant after the initial student's t-test.

Result

Of 120 under-five children with ALRI recruited, 73 (60.8%) were male and 47(39.7%) and the male/female ratio was 1.6:1. Forty-five (37.5%) of the children were aged between two and < 12months, 30(25%) between 12 and < 24 months, 23(19.1%), 6(5.0%), 16(13.4%) between 24 and < 36 months, 36 and <48 months, 48 and<60 months respectively. Nine (7.5) of the children had bronchiolitis, 16 (13.3)

lobar pneumonia and 95 (79.2) had bronchopneumonia. The mean (SD) age of the ALRI subjects with bronchiolitis was significantly lower than each of those with bronchopneumonia and lobar pneumonia {8.1(5.9) months *versus* 21.3(17.3) months, $p=0.025$; 8.1(5.9) months *versus* 25.0(20.7) months, $p=0.026$ respectively}. No such difference was identified between subjects with bronchopneumonia and lobar pneumonia {21.3(17.3) months *versus* 25.0(20.7) months, $p=0.444$ }.

Overall, the mean (SD) serum zinc level recorded in the children with ALRI was 18.7(11.8) $\mu\text{g/dl}$. The mean (SD) serum zinc level of 20.9 (15.5) $\mu\text{g/dl}$ in children with nasal discharge was significantly higher than the corresponding value for those without nasal discharge of 16.6 (6.5) $\mu\text{g/dl}$, $p=0.046$. The mean (SD) serum zinc level of 18.7(12.3) $\mu\text{g/dl}$ in children with difficult breathing was not significantly higher than the corresponding value of 18.4(6.5) $\mu\text{g/dl}$ in those without difficult breathing, $p=0.931$. No significant differences were found on comparing the mean (SD) serum zinc levels of the children with symptoms of vomiting, inability to eat/drink, restlessness, lethargy with those without these symptoms (each $p=0.346, 0.315, 0.521, 0.931$ respectively).

Table 1 shows the mean (SD) serum zinc levels based on the physical findings in the children with ALRI at presentation. Children with tachypnoea and crepitations had significantly lower mean serum zinc levels compared with those without these features ($p=0.014$ and **0.003** respectively). Children with grunting respiration had significantly higher mean serum zinc levels than the recorded value in those without grunting ($p=0.028$).

The clinical features of age-related tachypnoea, grunting respiration, presence of crepitations, remained statistically significant after a linear regression analysis (Table 2). The *goodness-of-fit* model gave an F -value of 7.116; $df=4$, $p=0.001$ and accounting for 19.8% effect on serum zinc levels. The presence of crepitations was identified as the strongest clinical feature associated with changes in the serum zinc levels in children with ALRI.

Table 2: Linear regression analysis of some clinical parameters of children with ALRI and their serum zinc levels

Parameter	Beta co-efficient	t	p -value
Nasal discharge	0.327	-0.092	0.831
Age-related tachypnoea	0.180	2.099	0.038
Grunting	-0.195	-2.254	0.026
Dehydration	0.103	0.152	0.941
Crepitations	0.310	3.667	0.001
Hepatomegaly	0.748	-0.030	0.919

Table 1: Serum zinc levels and the physical findings in children with ALRI

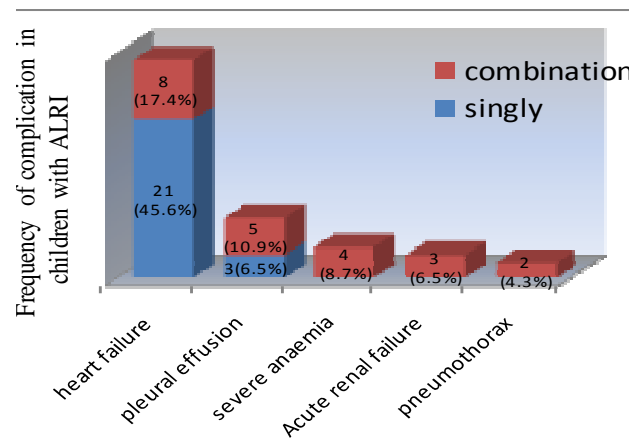
Physical findings	Present n (%)	Absent n (%)	t	p -value
Serum zinc ($\mu\text{g/dl}$)	Mean(SD)	Mean(SD)		
Dehydration	62(51.7) 16.7(8.6)	58(48.3) 20.8(14.3)	-1.903	0.059
Fever($\geq 37.5^\circ\text{C}$)	84(70.0) 19.1(11.0)	36(30.0) 17.6(13.7)	0.635	0.527
Pallor	28 (23.3) 17.6(8.7)	92(76.7) 19.0(12.6)	-0.549	0.584
Tachypnoea	112(93.3) 17.9(11.7)	8(6.7) 28.5(10.0)	-2.503	0.014
Central cyanosis	8(6.7) 17.8(4.8)	112(93.3) 18.7(12.2)	-0.207	0.837
Grunting	14(11.7) 25.2(21.1)	106(88.3) 17.8(9.9)	2.228	0.028
Wheeze	4(3.3) 24.0(1.62)	116(96.7) 18.5(12.0)	0.920	0.359
Snuffles	19(5.8) 21.6(15.6)	101(84.2) 18.1(11.0)	1.184	0.239
Rhinorrhoea	32(26.7) 21.0(14.0)	88(73.3) 17.8(10.9)	1.314	0.191
Nasal flaring	98(81.7) 18.5(12.6)	22(18.3) 19.4(7.8)	-0.321	0.745
Inter-costal recession	106(88.3) 18.1(10.6)	14(11.7) 23.1(18.7)	-1.494	0.138
Lower chest wall indrawing	69(57.5) 17.9(11.4)	51(42.5) 19.7(12.5)	-0.821	0.414
Head nodding	5(4.2) 19.7(6.0)	115(95.8) 18.6(12.0)	0.203	0.839
Abnormal percussion note	26(21.7) 18.0(7.5)	94(78.3) 18.8(2.8)	-0.304	0.762
Reduced breath sound intensity	112(93.3) 18.4(12.2)	8(6.7) 21.7(4.6)	-0.759	0.440
Crepitations	102(85.0) 17.3(10.5)	18(15.0) 26.3(15.9)	-3.066	0.003
Crepitations +rhonchi	6(5.0) 22.5(5.1)	114(95.0) 18.5912.1	0.803	0.423
Bronchial breath sounds	11(9.2) 20.7(7.8)	109(90.8) 18.5(12.2)	0.586	0.559
Hepatomegaly	44(61.7) 16.0(7.4)	76(38.3) 20.2(13.6)	-1.891	0.061

A total of 46 complications were recorded in 35 (29.2%) of the 120 children with ALRI; 24 (20.0%) had one complication and 11(9.2%) children had more than one complications. Figure 1 shows the overall distribution of these complications, with heart failure as the single most common complication.

Table 3 shows the mean (SD) serum zinc level in children with more than one complication was significantly lower than the mean level recorded in children who had one complication ($p = 0.020$).

Table 3: Relationship between complications of ALRI and serum zinc levels

Variable	n(%)	Serum zinc level (µg/dl) Mean(SD)	t	p-value
<i>Complication of ALRI</i>				
None	85(70.8)	18.0(12.8)	0.964	0.337
Present	35(29.2)	20.3(8.9)		
<i>Frequency of complication</i>				
One	24(68.6)	22.6(9.4)		
More than one	11(31.4)	15.2(5.0)	2.444	0.020

Fig 1: Complications among children with ALRI

Seven (5.8%) children died while 113 (94.2%) had partial or full recovery at discharge. Six (85.7%) of the fatal cases were males, and one (14.3%) was a female. Of the seven fatalities, four were infants while the remaining three were aged above 24 months. Five of the children that died had bronchopneumonia, and the other two had lobar pneumonia. None of the children with a final diagnosis of bronchiolitis died. All the seven fatalities had one or more ALRI-related complication.

The mean (SD) duration of admission among the survivors was 4.4 (2.3) days, while the corresponding data among the fatal cases was 7.6(3.8) hours. Table 4 shows the relationship between the serum zinc levels, the outcome of ALRI, and the duration of hospitalization among both the survivors and the fatalities.

Table 4: The relationship between serum zinc levels and duration of hospital stay among children with ALRI

Variable	n(%)	Serum zinc level (µg/dl) Mean (SD)	t	p-value
<i>Outcome of ALRI</i>				
Recovery	113(94.2)	18.8(12.1)	0.541	0.589
Death	7(5.8)	16.3(6.2)		
<i>Duration of hospital stay</i>				
<i>Among survivors (days)</i>				
≤4	80(69.0)	19.8(3.7)	1.423	0.158
>4	43 (17.7)	16.6(6.9)		
<i>Among fatality (hours)</i>				
≤8	5(71.4)	15.2(6.8)	-	0.502
>8	2(28.6)	19.1(4.5)	0.722	

Discussion

The findings of lower serum zinc levels in children with tachypnoea and crepitations compared to those without

these features is in accord with those of some earlier reports.¹³⁻¹⁵ These studies¹³⁻¹⁵ found that the children recruited as having ALRI based on the presence of tachypnoea and crepitations had lower serum zinc levels. Tachypnoea constitutes a valid avenue for an increase in energy expenditure. This can be ascribed to the increased work of breathing, higher insensible fluid loss and a reduction in the food intake associated with the respiratory distress.¹⁶ A combination of these tachypnoea-related phenomena could contribute to the low serum zinc levels. The presence of crepitations in ALRI probably reflects an ongoing inflammation in the lung parenchyma. This inflammatory process associated with pneumonia, and to a lesser extent in bronchiolitis, would contribute to the lower serum zinc levels recorded in subjects whom crepitations was identified as clinical signs of pneumonia.³ The associated acute phase reaction with the ongoing inflammation would also contribute to the lower serum zinc levels in those with crepitations.¹⁰ Also, the children may have had low pre-morbid serum zinc level which was further aggravated by the ongoing episode of ALRI.

The current finding of higher serum zinc levels in children with grunting respiration would appear to be inconsistent with an expectation of lower serum zinc levels in ALRI subjects with grunting respiration premised on the clinical import of the sign as an evidence of severe respiratory distress in severe pneumonia with or without associated pleural effusion.⁷ Although this finding appears superficially paradoxical, a plausible reason may be the possible effects of this self-administered form of achieving a peak end-expiratory pressure on the intrapulmonary vascular and tissue dynamics.¹⁶ By maintaining a high intrapulmonary pressure and with the frequent absence of tachypnoea, the high intrapulmonary pressure may conceivably engender higher serum zinc levels along with oxygen. In view of the current dearth of published data to substantiate this finding, there is a need for further studies with a larger sample size of children with grunting respiration to validate the current findings.

The predominance of heart failure as a complication of childhood pneumonia is consistent with the findings of earlier local hospital-based reports.^{7, 10, 17} Heart failure occurs due to the significant inflammation-driven reduction in the lung compliance associated with pneumonia and resultant right ventricular strain.⁷ The identification of lower serum zinc levels in subjects with more than one ALRI-related complication compared with the corresponding values in those without would suggest a zinc lowering effect of these complications. This may be related to the defective leucocyte phagocytic action due to zinc deficiency, with resultant failure to hinder intracellular multiplication of pathogens,³ and the subsequent unfettered dissemination of pathogens causing widespread damage and complications.

The case fatality among the children with ALRI in this series was 5.8% which is lower than the 7.8% recorded by Johnson *et al* in Ibadan,⁷ and the value of 10.0%

identified in an earlier study by Fagbule *et al* in Ilorin where the present study was carried out.¹⁰ The corresponding values from other countries included the 15.0% reported by Nathoo *et al*¹⁸ in Zimbabwe and 10.5% by Seghal *et al*¹⁹ in India which were also higher than the recorded value in the present study. The small decrease over the years in ALRI-related mortality may be possibly ascribed to a more prompt home recognition of disease severity, early diagnosis, better defined criteria for referrals, as well as the institutional adoption of more effective management strategies in the last few years.^{19,20} About 70% of the fatal cases were accounted for by bronchopneumonia, thus constituting the single most important contributor to ALRI case fatality in the current study. This observation is in accord with the earlier reports emanating from South-West and North-Central Nigeria,^{6, 7, 10, 21} as well as those from other developing countries.^{11, 18} However, the import of this observation is difficult to ascertain in view of the fact that bronchopneumonia was the most common admission diagnosis, accounting for almost 80.0% of the ALRI syndromes diagnosed at recruitment.

There was a paucity of published studies documenting the relationship between the serum zinc levels and outcome in children with ALRI for comparison however, the present study found that neither the duration of hospitalization nor the outcome of admission were significantly affected by the serum zinc levels. This might be due to a limitation in the number of cases analyzed for this outcome variable. It is however of clinical significance as survivors with longer hospital stay had lower zinc levels while lower serum zinc levels were identified in those with a shorter hospital stay among the fatal cases. One or more ALRI-associated complication was identified among all cases with a fatal outcome, thus suggesting a zinc lowering effect with increased severity of ALRI and related complications. However, the

paucity of published data to compare with would hardly enable this author to draw firm inferences from this observation. Also, the pre-morbid serum zinc levels of the children recruited were not determined in the current study. Hence, more studies would be required in future to determine the trend of changes in serum zinc levels with regard to the disease outcome of ALRI in children.

Conclusion

The presence of crepitations had the strongest clinical association with a low serum zinc level. No significant difference was identified between the mean serum zinc level of the children who recovered and those that died. Children managed for ALRI would likely benefit from post-treatment zinc supplements and appropriate zinc-rich sources of food at discharge.

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Ibraheem RM: did the final draft of this paper.

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