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Role of vitamin D, serum zinc, and serum iron deficiency in community-acquired pneumonia in children

Asmaa Alhusseiny Ahmed Alsharkawy[1] and Ahmed R. Rezk[2*]

Abstract

Background: Community-acquired pneumonia is a major cause of death among children. Inadequate nutrition disrupts the immune system and increases the susceptibility to infections. We aimed to evaluate the association between vitamin D, serum zinc, and iron, and pneumonia. A case-control study was conducted at the outpatient clinic and emergency room of Children's Hospital. Thirty-one patients with community-acquired pneumonia and 36 healthy children (control group) underwent serum sampling for vitamin D, zinc, and iron.

Results: Most patients had mild form (n = 17, 54.8%). All patients survived and were discharged. The serum iron level showed a non-significant difference between pneumonia and control groups (p > 0.05). TIBC, vitamin D, and serum zinc were significantly lower in the patient group than the control group (P value = 0.04, < 0.001, and 0.03, respectively). Vitamin D deficiency was highly associated with the severity of pneumonia (P value = 0.008).

Conclusion: Adequate serum zinc and vitamin D levels may be protective against infection with community-acquired pneumonia in children aged from 2 months to 5 years old, but not iron.

Keywords: Community-acquired pneumonia, Iron, Pediatrics, Vitamin D, Zinc

Background

Community-acquired pneumonia (CAP) is defined as an acute infection of the pulmonary parenchyma in a previously healthy child who has not resided in a hospital in the preceding 14 days [1]. Approximately, 150 million cases of childhood community-acquired pneumonia have been reported each year [2]. Pneumonia remains the major single cause of death in children outside the neonatal period, causing approximately 900,000 of the estimated 6.3 million child deaths in 2013 [1]. In Egypt, the incidence of pneumonia has been estimated at 0.1-0.2 pneumonia episodes per child-year [3]. Inadequate nutrition and acute lower respiratory infection are overlapping and interrelated health problems affecting children in developing countries [4].

Vitamin D has many important functions not only for calcium and bone homeostasis but also for immunity and antimicrobial response. For innate immunity, macrophages recognize pathogen-associated molecular patterns such as lipopolysaccharides and flagellin by toll-like receptors (TLR). TLR binding leads to a series of events that result in the production of bactericidal peptides such as cathelicidin and beta-defensin 4, and it also increases the expression of vitamin D receptors [5]. Vitamin D binding enhances the transcription of the genes of cathelicidin and beta-defensin 4 [6]. Vitamin D deficiency in addition to its relation to the development of rickets has been reported to be a major risk factor for CAP [2].

Iron is a necessary element for immune system integrity. It is important for immune cell proliferation and differentiation and enzyme production against pathogens [7]. Its deficiency has been related to many infections including CAP [8].

* Correspondence: ahmed_rezk@med.asu.edu.eg
[2]Department of Pediatrics, Intensive care unit, Ain Shams University Hospitals, Cairo, Egypt
Full list of author information is available at the end of the article

Table 1 Characteristics of the study population

		Patient group (*N* = 31)	Control group (*N* = 36)	Test value	*P* value
Age (months)	Median (IQR)	12 (4-17)	10.5 (6-26)	−0.327**	0.743
Sex	Male	15 (48.4%)	17 (47.2%)	0.009*	0.924
	Female	16 (51.6%)	19 (52.8%)		
Weight centile	Median (IQR)	50 (25-50)	75 (50-90)	−3.246**	0.001′
Height centile	Median (IQR)	25 (25-50)	50 (50-75)	−3.441**	0.001′
Type of feeding	Breast	11 (35.5%)	8 (22.2%)	3.756*	0.289
	Artificial	3 (9.7%)	8 (22.2%)		
	Weaned	12 (38.7%)	17 (47.2%)		
	Mixed	5 (16.1%)	3 (8.3%)		

*Chi-square test
**Mann-Whitney

Zinc is an essential nutrient for normal immune system activity [9]. Zinc deficiency is associated with increased risk of infection, particularly pneumonia and diarrhea [10]. Children are more prone to zinc deficiency and this is attributed to the fact that they are less able to absorb dietary zinc and some children, especially in low-income countries, may not have received enough zinc from their mothers before birth [11].

In our study, we aimed to assess the association between serum zinc, iron, and vitamin D deficiency and community-acquired pneumonia among children. We, also, targeted to identify the most related nutrient deficiency to infection development and progression.

Methods

This case-control study included 67 individuals, 31 with community-acquired pneumonia and 36 healthy (control group), admitted at the outpatient clinic and emergency room of Children's Hospital, from January 2019 to June 2019. Informed consent was obtained from the parents or guardians of all participants for admission to the hospital and the procedures performed during hospitalization. Ethical approval was obtained from the research ethics board. This study was conducted under the Declaration of Helsinki.

Inclusion criteria were patients aged 2 months up to 5 years who suffered CAP according to British Thoracic Society (BTS) criteria [12]. Patients were clinically classified according to the severity of pneumonia. Mild to moderate cases had temperature < 38.5 °C, respiratory rate < 50 breaths/min, and mild breathlessness. Severe cases had temperature ˃ 38.5 °C, respiratory rate ˃ 50 breaths/min, severe difficulty in breathing, nasal flaring, cyanosis, and tachycardia according to age. We excluded patients with nosocomial pneumonia or any cardiac, neurological, musculoskeletal, hepatic, or renal disease.

All participants were exposed to detailed medical and breastfeeding history, complete clinical examination. Investigations included chest X-ray anteroposterior view, complete blood count using Sysmex KX-2IN automated hematology analyzer, and C-reactive protein using Avitex CRP latex. We measured serum calcium, phosphate, and alkaline phosphatase in addition to vitamin D3 levels using high-performance liquid chromatography (HPLC). Serum zinc level measurement was done on a 5010-spectrophotometer supplied by Roche Diagnostics (GmbH, Sandhofer Strasse 116, D-68305 Mannheim) using zinc fluid monoreagent supplied by Centronic GmbH (Kleinfeld 11, 85456 Wartenberg/Germany).

Serum iron assay analysis was done on a 5010-spectrophotometer supplied by Roche Diagnostics using a total iron chromazurol B single reagent supplied by Spectrum (Schiffgraben 4130175 Hannover, Germany). Serum TIBC analysis was done on a 5010-spectrophotometer supplied by Roche Diagnostics (GmbH, Sandhofer Strasse 116, D-68305 Mannheim) using saturation and precipitation methods supplied by GPL (CHEMELEX, S.A. Pol. Ind. Can Castells. C/Industrial 113, Nau J – 08420 Canovelles –BARCELONA – SPAIN). Transferrin saturation percentage was calculated as the value of serum iron divided by the total iron-binding capacity of the available transferrin. We excluded serum ferritin despite it is the most specific for identifying iron deficiency anemia as it is an acute-phase reactant, and its levels may be elevated under certain conditions such as infection and inflammation.

Table 2 Distribution of severity, and fate, and mortality among the patient group (*n* = 31)

		No.	%
Severity	Mild	17	54.8%
	Moderate	10	32.3%
	Severe	4	12.9%
Fate and mortality	Admitted again	1	3.2%
	Discharged	30	96.8%

Table 3 Serum iron, TIBC, transferrin saturation, and adequacy of iron level and TIBC compared to normal levels

		Patient group No. = 31	Control group No. = 36	Independent *t* test	
				t	*P* value
S. iron (μg/dL)	Mean ± SD	127.54 ± 31.68	138.17 ± 40.39	−1.185	0.240
Iron level	Adequate	31 (100.0%)	36 (100.0%)	NA	NA
	Inadequate	0 (0.0%)	0 (0.0%)		
TIBC (μg/dL)	Mean ± SD	580.05 ± 126.68	519.69 ± 109.43	2.093	0.040
TIBC	Adequate	4 (12.9 %)	8 (22.2%)	0.984	0.321
	Inadequate	27 (87.1%)	28 (77.8%)		
Transferrin saturation	Mean ± SD	0.26 ± 0.10	0.24 ± 0.08	0.643	0.522

Statistical analysis

The collected data were revised, coded, tabulated, and computed using Statistical Package for Social Science (IBM SPSS) version 15 using appropriate statistical methods. Data were presented as mean, standard deviation, and range when parametric and median with interquartile range with non-parametric. For quantitative data with parametric distribution, an independent *t* test and one-way analysis of variance (ANOVA) were employed, while for non-parametric data, the Mann-Whitney test was used. Categorical variables were compared using the Chi-square test. Power analysis was performed before patient recruitment to validate that the sample size was sufficient to back the statistical significance of the study outcomes with a confidence interval of 95% and a margin of error of 5%. A P value ≤ 0.05 was considered statistically significant.

Results

The study was conducted on 67 participants; 15 males and 16 females were in the patient group, and 17 males and 19 females were in the control group. The difference in age, sex, and type of feeding between the two groups were insignificant (P values > 0.05) but the weight and height were significantly lower among the patient group (Table 1).

Table 2 demonstrates the severity level of pneumonia among the patient group, most patients had mild form (n = 17, 54.8%). All patients survived and were discharged.

Serum iron level and transferrin saturation demonstrated a non-significant difference between the pneumonia group and the control group. However, TIBC was significantly lower in the patient group than in the control group (P value = 0.04). All subjects in our study had adequate serum iron levels (Table 3).

Vitamin D and serum zinc were significantly lower in the patient group than the control group (p value < 0.001 and 0.03, respectively) (Tables 4 and 5).

Among the patient group, the levels of serum iron, TIBC, and transferrin saturation were not related to the severity level of pneumonia (P values > 0.05) as well, the levels of serum zinc, calcium, phosphate, and alkaline phosphatase. However, vitamin D deficiency was highly associated with the severity of pneumonia (Table 6). Table 7 shows that all patients with severe pneumonia had deficient vitamin D.

In Table 8, the combined inadequacy of vitamin D and TIBC was significantly low in the patient group suggesting their strong association in pneumonia development.

Discussion

Pneumonia is one of the major causes of childhood death. Many factors have an impact on the pathogenesis and clinical course of pneumonia. We targeted to evaluate the effect of serum iron, vitamin D, and zinc deficiency and identify the most related nutrient deficiency to pneumonia.

In our study, we evaluated the iron profile and the possible impact on pneumonia. We found that 64.5% of

Table 4 Serum vitamin D level and comparison to normal range

		Patient group No. = 31	Control group No. = 36	Independent *t* test	
				t/X^2*	*P* value
Vit. D (nmol/L)	Mean ± SD	37.32 ± 20.56	82.50 ± 30.74	−6.949	0.000'
Vit. D level	Sufficient	6 (19.4%)	31 (86.1%)	32.254*	0.000′
	Insufficient	13 (41.9%)	5 (13.9%)		
	Deficient	12 (38.7%)	0 (0.0%)		

*Chi-square test

Table 5 Serum zinc level and comparison to normal range

		Patient group No. = 31	Control group No. = 36	Independent *t* test	
				t	*P* value
S. zinc (μg/dL)	Mean ± SD	114.29 ± 45.01	145.01 ± 64.69	−2.220	0.030′
Zinc level	Adequate	25 (80.6%)	33 (91.7%)	1.740	0.187
	Inadequate	6 (19.4%)	3 (8.3%)		

cases had hemoglobin level < 11gm/dl which might indicate a strong association between iron deficiency anemia and the CAP. El-Sakka et al. stated that a low hemoglobin level is a risk factor for acute lower respiratory infections as it was detected in 62.5% of pneumonia patients [13]. Similarly, Hussain et al. reported that 64.5% of their hospitalized patients and 28.2% of the healthy controls were anemic and that the anemic children were 4.6 times more susceptible to lower respiratory tract infection [14].

In the current study, there was no relation between hemoglobin level and the severity of pneumonia (Table 6). In contrast, Coles, Malla, and Shallans' studies reported an association between low hemoglobin levels and pneumonia severity [15–17].

In our study, there was no association between serum iron level and community-acquired pneumonia; however, the TIBC was more in the pneumonic group. Although these findings may be against the physiological facts during infection, yet maybe the small sample size and other causes of anemias had an effect. (Table 3)

Vitamin D was significantly lower among the patient group than in the control group (Table 4). Vitamin D levels correlated with the severity of pneumonia in the studied population (Table 6). Kulkarni and Chougule as well as Jovanovich et al. reported that there was a high association between vitamin D deficiency and community-acquired pneumonia in pediatrics [18, 19].

A study noted that 74% of children with severe pneumonia had rickets as defined by low or normal calcium, low phosphorous, and high serum alkaline phosphatase [20]. Even subclinical vitamin D deficiency was found to be associated with severe acute lower respiratory infection in children less than 5 years of age [21]. The association of vitamin D deficiency and lower respiratory tract infections is not only limited to children but is also found among newborns, infants, and adults [22].

Zinc level was significantly lower in the patient group than in the control group which means that inadequate serum zinc level is associated with community-acquired pneumonia (Table 5). A study reported that the zinc level in peripheral blood was reduced in 76% of critically ill infants with community-acquired pneumonia [23]. Barnett et al. found that zinc supplementation had a beneficial effect on the clinical course and incidence of pneumonia [24]. Also, Arica et al. demonstrated that there was a significant relationship between the plasma levels of zinc and the susceptibility to pneumonia in children aged 0-24 months; moreover, zinc may be more protective in children whose immune systems are not fully developed [25]. Another study reported that high levels of zinc in pediatric patients with pneumonia could lower the incidence and prevalence of pneumonia, days of hospitalization, and improve the clinical outcome [26].

In contrast, Saleh et al. reported that there is no relation between zinc levels and community-acquired pneumonia [27]. Also, on the contrary, Vinayak and Behal found that a course of zinc supplementation

Table 6 Laboratory values among the patient group are classified according to pneumonia severity

	Mild (*n* = 17)	Moderate (*n* = 10)	Severe (*n* = 4)	One-way ANOVA test value	*P* value
Hemoglobin	10.10 ± 1.23	10.95 ± 1.40	0.18 ± 0.92	1.496	0.241
Iron (μg/dL)	125.67 ± 30.49	133.67 ± 31.67	120.15 ± 43.00	0.311	0.735
TIBC (μg/dL)	526.31 ± 130.00	516.24 ± 44.65	500.18 ± 151.13	0.094	0.911
Transferrin saturation	0.26 ± 0.12	0.26 ± 0.06	0.26 ± 0.14	0.002	0.998
Vit. D (nmol/L)	47.12 ± 22.92	27.20 ± 7.50	21.00 ± 4.24	5.811	0.008
Zinc (μg/dL)	105.65 ± 46.65	125.34 ± 33.81	123.38 ± 65.44	0.681	0.514
Ca^{2++} (mg/dl)	8.20 ± 1.40	8.04 ± 1.39	9.08 ± 0.68	0.896	0.419
Phosphate (mg/dl)	4.67 ± 1.42	4.75 ± 0.63	3.75 ± 1.32	1.091	0.350
Alkaline phosphatase (IU/L)	313.88 ± 150.89	296.50 ± 119.93	223.25 ± 75.28	0.729	0.491

Table 7 Serum iron, serum vitamin D, and serum zinc levels compared to normal range in different severity of pneumonia

		Mild (*n* = 17)	Moderate (*n* = 10)	Severe (*n* = 4)	Chi-square test value	*P* value
Iron level	Adequate (60-170μg/dl)	17 (100.0%)	10 (100.0%)	4 (100.0%)	NA	NA
	Inadequate	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Vit. D level	Sufficient (˃ 60 nmol/L)	6 (35.3%)	0 (0.0%)	0 (0.0%)	15.360	0.004
	Insufficient (30-60 nmol/L)	9 (52.9%)	4 (40.0%)	0 (0.0%)		
	Deficient (˂ 30 nmol/L)	2 (11.8%)	6 (60.0%)	4 (100.0%)		
Zinc level	Adequate (70-120μg/dl)	12 (70.6%)	10 (100.0%)	3 (75.0%)	3.583	0.167
	Inadequate	5 (29.4%)	0 (0.0%)	1 (25.0%)		

Table 8 Comparison between patient and control groups as regard combined zinc and vitamin D inadequate levels, combined zinc and TIBC inadequate levels, combined vitamin D and TIBC inadequate levels, inadequate all of them, and sufficient all of them

	Patient group		Control group		Chi-square test	
	No.	%	No.	%	X^2	*P* value
Combined inadequate zinc and vit. D	0	0.0%	0	0.0%	0.000	1.000
Combined inadequate zinc and TIBC	2	6.5%	2	5.6%	0.024	0.877
Combined inadequate vit. D and TIBC	17	54.8%	4	11.1%	14.800	0.000
Inadequate zinc, vit. D, and TIBC	2	6.5%	1	2.8%	0.526	0.468
Inadequate one of them	10	32.3%	21	58.3%	4.555	0.033
Sufficient all of them	0	0.0%	8	22.2%	7.823	0.005

for patients with pneumonia, aged up to 5 years, did not have a significant effect and recommended that it should not be proposed for adjuvant therapies and so no relation between serum zinc level and pneumonia [28].

We found that serum vitamin D is the most important single relative risk factor for acquiring CAP in comparison to the zinc level followed by TIBC (Table 8).

The results of the current study are limited by the small sample size, short duration of follow-up, and the lack of age subgrouping. Further studies are recommended to ensure the accuracy of our findings.

Conclusion

In the view of our study, we can conclude that adequate serum zinc, vitamin D levels may be protective against infection with community-acquired pneumonia in children aged from 2 months to 5 years old. However, we could not prove that adequate serum iron levels may reduce community-acquired pneumonia affecting the same age group. We recommend supplementation of zinc, vitamin D, and iron to maintain the integrity of the immune system and as prophylaxis against pneumonia.

Abbreviations

CAP: Community-acquired pneumonia; BTS: British Thoracic Society; TIBC: Total iron blood capacity; TLR: Toll-like receptor

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Authors' contributions

AA has put the study design, collected data, and shared in drafting. AR shared in the study design, drafted the manuscript, and performed the statistical analysis. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Obtained from Ain Shams University, Faculty of Medicine, Research Ethics Board ID number 30-19-872. Written informed consent was obtained from the parents of each child enrolled in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Pediatrics, Chest Unit, Ain Shams University Hospitals, Cairo, Egypt. [2]Department of Pediatrics, Intensive care unit, Ain Shams University Hospitals, Cairo, Egypt.

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