

Comparison of Respiratory Rate in Children having Pneumonia with and without Rickets

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Abstract

Objective: To compare the duration for stabilization of respiratory rate in children having pneumonia with and without rickets.

Methods: This case control study was conducted at Department of Paediatrics Dow University of Health Sciences and Civil Hospital Karachi, Pakistan, from January to August 2016. In this study 100 diagnosed cases of pneumonia with age group of >2 months to 60 months were divided into two equal groups as cases and control. Those children with pneumonia who had any clinical sign of rickets had an X-ray wrist and serum levels of alkaline phosphatase done to confirm the diagnosis of rickets. Children who were confirmed to have rickets along with pneumonia were recruited as "cases" while "controls" had pneumonia but without rickets. Patients were followed as per Integrated Management of Neonatal and Childhood Illnesses (IMNCI) guidelines and respiratory rate was noted daily along with other features of pneumonia until it returned to normal for age as per guidelines.

Results: The total of hundred patients was divided into two equal groups as cases and controls. Out of 100 patients 59% were male and 41% were female. Over all mean \pm SD for stabilization of fast breathing was 4.38 ± 2.39 days and highly significant difference was found in stabilization of respiratory rate between cases and controls, $p < 0.0001$). Mean \pm SD of the weight was 7.31 ± 3.46 kg. Most of the patients 47% were in the age group of 2-12 months of age.

Conclusion: Patients having pneumonia with concomitant rickets takes significantly longer to revert to their normal respiratory rate as compared to those with pneumonia but no rickets.

Keywords: Pneumonia, rickets, respiratory rate, vitamin D deficiency, paediatrics

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Introduction

Pneumonia is the most important cause of morbidity and mortality in children under the age of 5 years all over the world¹. One of the significant risk factors for severe pneumonia in Indian children

was found to be vitamin D deficiency² which is also seen very frequently in our community as well. According to one study the frequency of rickets was found to be 2.25% among admitted paediatric patients in Pakistan³. This association of pneumonia with vitamin D deficiency or nutritional rickets is well documented in literature by various studies from many countries including Pakistan⁴⁻⁷ and it has been observed that rachitic infants are commonly hospitalized due to lower respiratory tract infections⁸. Although the association of rickets and vitamin D deficiency (VDD) with pneumonia is now well documented in literature, the effect of rickets on the outcome of pneumonia has not been studied so far⁹. Fast breathing or tachypnoea is considered the most consistent sign of pneumonia in the world

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literature including the Integrated Management of Neonatal and Childhood Illnesses (IMNCI) guidelines¹⁰, where it not only makes the basis for diagnosis of pneumonia but is also taken as the outcome measure of the treatment of pneumonia. It was being commonly observed that the patients who were admitted in our paediatric department with the diagnosis of severe pneumonia were taking longer to recover especially in the context of fast breathing when they had associated rickets than the ones without rickets, thus requiring a change of antibiotics several times before the patient could be considered treated on the basis of return of their respiratory rate to normal values. In order to prove our observation, we decided to study the effects of rickets on the duration of persistence of fast breathing in severe pneumonia in admitted pediatric patients. By confirming the association, we may make recommendations regarding the change in the duration of treatment of pneumonia in patients with concomitant rickets and thus prevent the unnecessary use of multiple antibiotics over prolonged periods of time contributing to prolonged hospital stay, increased expenses and probability of increasing antibiotic resistances. We may further recommend the studies to clarify if this persistence is due to slower resolution of infection or other factor related to vitamin D deficiency. Depending on the results we may also recommend the inclusion of vitamin D in the standard treatment of pneumonia.

Patients and Methods

This observational, case-control study was conducted at Department of Paediatrics Dow University of Health Sciences and Civil Hospital Karachi, Pakistan, from January to August 2016. Sample was calculated on the basis of pilot study through openepi sample size calculator using Mean \pm SD of stabilization of respiratory rate in cases and controls (5.80 ± 2.39 vs. 2.96 ± 2.22), Power of test ($1 - \beta$) = 80% , level of significance 95% then the estimated $n=11$ in each group. But it was extended to total $n=100$ children, $n=50$ in each group of cases and controls. The total sample size was hundred (100) patients and divided into two equal groups i.e. $n=50$ in each group as cases and controls. Non-probability consecutive sampling method was used for sample selection. Children >1 month to <5 years of age of either gender admitted as in-patients with acute lower respiratory infection (ALRI) or pneumonia were included in the study, after taking informed verbal consent from parents/guardians. Recruitment was incidental with frequency matching. Patients with known underlying chronic lung

diseases e.g cystic fibrosis, bronchiectasis, Kartagener's syndrome, immotile cilia syndrome, emphysema, bronchial asthma, gastroesophageal reflux disease (GERD), underlying heart disease or children with other underlying co-morbid conditions were excluded. Pneumonia was defined as the presence of fever and/or acute respiratory symptoms and/or evidence of parenchymal infiltrates on a chest radiograph. Clinical signs of rickets included widening of wrist, frontal bossing, parietal bossing, and wide anterior fontanel for age, bowing of legs, knock knees (genu valgum). Those children with pneumonia who had any clinical sign of rickets had an X-ray wrist and serum levels of alkaline phosphatase done to confirm the diagnosis of rickets. Children who were confirmed to have rickets along with pneumonia were recruited as "cases" while children with pneumonia but without rickets were recruited as "controls". Both cases and controls were treated similarly for pneumonia as per standard recommendation of the WHO¹⁰. Patients having rickets were given additional standard treatment for the vitamin D deficiency. Patients were followed as per Integrated Management of Neonatal and Childhood Illnesses (IMNCI) guidelines¹⁰. Respiratory rate was observed daily until it returned to normal for age as per following standard definitions of fast breathing; respiratory rates ≥ 50 /min in children 2 months to <12 months, ≥ 40 /min in children 12 months to <60 months. When tachypnoea subsided then the treatment of pneumonia was considered as successful. Statistical package for social sciences (SPSS version 20) was used for analysis of collected data. Mean \pm SD were calculated for age, weight and duration of stabilization of fast breathing in days. Frequency and percentage were calculated for gender. Independent sample t-test was applied to compare both the groups. Analysis of variance (Anova) was applied to assess the significant difference between the age groups considering, $p \leq 0.05$ as significant.

Results

The study included hundred paediatric patients having pneumonia with age >2 months to 60 months. Children were divided into two equal groups i.e. 50 cases with rickets and 50 controls without rickets. Over all mean age and weight of the patients were 17.19 ± 14.83 months and 7.31 ± 3.46 kg respectively. The most common age group was 2 to 12 months. Males were more commonly affected than females; the male to female ratio being 1.4:1 (Table 1).

Overall time taken till normalization of fast breathing was 4.38 ± 2.39 days. Mean days required for return of this fast breathing to normal rate were significantly lower in controls (2.96 ± 2.22) as compared to cases (5.80 ± 2.39) with $p < 0.0001$ as shown in Table 2.

Most of the patients belonged to the age group of 2 to 12 months (23 cases vs. 24 controls). The difference of mean days between the cases and controls needed for return of respiratory rate to normal was highly significant among the three age groups ($p < 0.00001$) as well as within the group as shown in (Table 3). The difference was longest in the age group of 12 to 60 months (6.84 ± 2.36 vs. 4.10 ± 2.57).

Table 1. Demographic Characteristics of the Patients (n=100)

Age in months	Frequency
1-2	15 (15%)
2-12	47 (47%)
12-60	38 (38%)
Mean \pm S D	17.19 ± 14.83
95% C.I	12.97-21.40
Gender	Frequency
Male	59 (59%)
Female	41 (41%)

Table 2. Comparison of Stabilization of respiratory rate (n=100)

Group	Mean \pm SD	95% C.I
Cases (n=50)	5.80 ± 2.39	5.12-6.47
Controls (n=50)	2.96 ± 2.22	2.32-3.59
p-Value	0.0001*	

Table 3. Comparison of Stabilization of respiratory rate with respect to age group (n=100)

Age group (in months)	Frequency	Mean \pm SD	p-Value (within group)
Cases (n=50)			
1-2	8 (16%)	4.62 ± 1.18	0.037
2-12	23 (46%)	5.34 ± 2.46	
12-60	19 (38%)	6.84 ± 2.36	
Controls (n=50)			
1-2	7 (14%)	1.57 ± 0.78	0.008
2-12	24 (48%)	2.45 ± 1.79	
12-60	19 (38%)	4.10 ± 2.57	
p-Value(between groups)		0.00001*	

Applied Analysis of Variance (Anova)

Discussion

Being involved in the regulation of about 1000 human genes vitamin D has actions other than its well-known functions related to bone and calcium homeostasis especially prevention and treatment of rickets in children. Vitamin D insufficiency has been implicated in a number of immune related illnesses including multiple sclerosis, type 1 diabetes, and cancer¹²⁻¹³ as well as respiratory diseases such as asthma¹⁴⁻¹⁶. It has also been shown to have an important role in the innate immune system by virtue of regulating the inflammatory response and attracting immune cells to infection sites, binding and neutralizing lipopolysaccharides, and promoting re-epithelialization. It also stimulates the secretion of natural antibiotics known as antimicrobial peptides including LL-37, which is highly expressed at barrier sites including respiratory and colonic epithelia, saliva and skin, thus providing an important first line defense mechanism against the infectious agents including those causing pneumonia. There is increasing evidence that the serum 25(OH)D levels of at least 75 nmol/L rather than 25-50 nmol/L are the appropriate concentration required for increased production of LL-37⁷. Although this evidence explains the association of rickets and vitamin D deficiency (VDD) with pneumonia, which is now well-documented in literature, the studies regarding the effect of rickets on the severity and outcome of pneumonia are sparse⁹. It has been reported by Leow L et al, that people who have very low levels of vitamin D levels are more likely to have worse outcomes and longer recoveries than people with higher levels of vitamin D¹⁷. Similar observation was shared by Banajeh SM who concluded that children with rickets were four times more likely to have a slower recovery from pneumonia than children with higher vitamin D levels⁹. Evidence of links between rickets/vitamin D3 deficiency and worse outcome of pneumonia were also reported from Netherlands¹⁸. Germany¹⁹, Amman and Jordan⁸ documenting higher chances of hospitalization and increased mortality with the illness, increased severity of pneumonia and significantly longer hospital stay of rachitic infants than non-rachitic ones. Similar observation

was shared by Tezer H, Siklar Z et al, in Turk J Pediatr reporting a significantly longer hospital stay in the rachitic infants with pneumonia than the non-rachitic control group (9.5 days vs. 7.4 days, $p = 0.002$)²⁰. The results of our study are also in agreement with those of the above mentioned researches showing that respiratory rate of the cases who had pneumonia with concomitant rickets took significantly longer to revert to normal than the ones who had pneumonia but no rickets. Additionally the predominance of male gender with male to female ratio of 1.4:1 and the mean age of 13.04 ± 04 with 2-12 months being the most affected age in our study are also in agreement with other observations shared in literature²¹⁻²⁵.

Contrary to all these studies showing consistent results, there is another study which did not find any correlation between the duration of resolution of pneumonia symptoms and levels of vitamin D and LL-37. The explanation put forth was that LL-37 plays a role in the defense against infection but once infection has taken place, other factors determine its course and whether it will resolve or not⁷. To support this explanation are other studies one of them analytical from Kabul which showed that children who were supplemented with vitamin D along with treatment of pneumonia survived longer without having recurrences of the illness²⁵. There are other researchers who think that vitamin D level may not only decide whether or not someone develops pneumonia but may also be a factor to determine how severe their symptoms may be²⁶. The researchers conclude that having high vitamin D levels may be linked to better outcomes and survival from pneumonia¹⁸. In our study, we are able to prove that fast breathing persists longer in patients diagnosed with pneumonia with concomitant rickets, however, limitations of the study include being unable to decide if this persistence of fast breathing is due to delayed resolution of pneumonia or some other factor related to rickets. Furthermore this is a hospital-based study with convenient sampling so the results cannot be generalized. Being hospital-based study it does not include the patients with milder pneumonia who were treated at the outpatient de-

partment of the respective hospital. Hence, further studies need to be done before before recommendations, regarding the change in the duration of treatment of pneumonia in patients with concomitant rickets can be made.

It is recommended that further studies be done to clarify if this persistence of fast breathing in patients of pneumonia with concomitant rickets is because of delayed resolution of pneumonia or some other factor related to rickets. Also, large scale, multicenter studies to determine the frequency/prevalence of vitamin D insufficiency in early infancy after which we could include routine vitamin D supplementation in all infants to prevent consequent rickets and other complications associated with it. Furthermore, randomised control trials should be done, indicating whether or not taking vitamin D supplements can help to prevent pneumonia or its fast resolution.

Conclusion

We conclude that patients having pneumonia with concomitant rickets take significantly longer to revert to their normal respiratory rate than the ones with pneumonia but no rickets. Whether this prolongation of tachypnea in these patients is actually because of slow resolution of pneumonia itself or some other reason needs to be addressed by further studies.

Conflict of Interest

Authors have no conflict of interests and no grant/ funding from any organization for this study.

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