Vitamin D levels in Children with Recurrent Wheezing: An Observational Study

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Abstract

Aim: To study the vitamin D levels in toddlers with recurrent wheezing.

Methods: In this prospective observational study, 108 children aged 1-3 years with recurrent wheezing and 41 healthy age and sex matched controls were included. The clinical, demographic, socio-economic, food habits, and sun exposure of both the groups were assessed. The serum levels of vitamin D were measured and Asthma predictive index (API) of all the cases was calculated. Spearman or Pearson correlation coefficients were used to see relationship of different variables with Vitamin D.

Results: Among 108 cases and 41 controls we enrolled, majority of them had vitamin D deficiency or insufficiency. The difference in vitamin D levels in the two groups was not statistically significant (p=0.0619). We found no significant difference in the vitamin D levels between, urban and rural population, vegetarians and non-vegetarians, adequately and inadequately sun light exposed children. There was also no correlation between the vitamin D levels and the number of wheezing episodes in the last 1 year. There was no significant correlation between the number of criteria of API positive and the vitamin D levels.

Conclusion: Our study showed that the overall prevalence of vitamin D deficiency is very high among toddlers with recurrent wheezing. We conclude that vitamin D rich diet and sunlight exposure cannot prevent vitamin D deficiency in Indian toddlers. National programme for universal supplementation of vitamin D is required to control this epidemic of vitamin D deficiency.

Introduction

Recurrent wheezing is a common complaint in pediatric population and some studies have shown that more than thirty per cent children have at least one episode of wheezing prior to the completion of the third year of life, with a prevalence of more than fifty percent at the age of 6 years(1). Asthma is considered to be the most common cause of wheezing, however, most of the pediatric cases of wheezing doesn’t develop asthma in later life(2). There has been significant research on the mechanisms and the role of vitamin D, in the development of lung and immune system, both in-utero and in the post-natal life. Vitamin D deficiency has been implicated as a risk factor for developing asthma and pulmonary diseases in many studies(3–5). Some recent studies in the pediatric population, showed that Vitamin D3 used therapeutically in asthmatics gives benefit by reducing number of exacerbations, requirement of steroids, reduction in rates of hospitalization and improvement in spirometry(6–9). While most published studies report a protective effect of a higher vitamin D levels or a higher vitamin D intake, there are some studies which suggest adverse outcomes also(10, 11).

The Asthma Predictive Index, developed based on the Tucson cohort, is a well-known predictor of school age asthma, in children less than three years with recurrent wheezing. Its specificity is high (97%) but sensitivity is low (16%)(12).The Index is either positive or negative. A positive API score requires recurrent episodes of wheezing during the first 3

years of life and 1 of 2 major criteria (physician-diagnosed eczema or parental asthma) or 2 of 3 minor criteria (physician diagnosis allergic rhinitis, wheezing without colds, or peripheral eosinophilia > 4%). The most important aspect of API, compared to the other asthma predicting scores developed subsequently like Isle of Wight, PIAMA etc., is its ability to rule out the possibility of developing asthma by school age in children with recurrent wheezing(13). In the last few years though, some studies have shown association of low or high vitamin D level with wheezing disorders such as asthma in pre-school and school going in children, there are very few studies which have investigated this association in toddlers. To the best of our knowledge this is the first study to calculate the Asthma Predictive Index in Indian children.

In India, recurrent wheezing is a very common problem in infants and preschool children. If a direct association is found between Vitamin D deficiency and recurrent wheezing and its severity, an intervention can be planned with Vitamin D supplementation. Children with positive Asthma Predictive Index can be followed more vigilantly and can be started on early maintenance therapy relatively earlier if required.

Methods

We recruited 108 subjects and 41 controls of the age group one year to three years over a period of one year from March 2014 to March 2015 from the Pediatric Emergency and the Allergy and Asthma clinic of Advanced Pediatric Centre, Post Graduate Institute of Medical Education & Research, Chandigarh. The study was approved by the Institute Ethics Committee, PGIMER Chandigarh.

Children of the above-mentioned age group with greater than two episodes of wheezing in the last six months or greater than three episodes of wheezing in the last one year were considered as Recurrent Wheezers and included in our study. Children were excluded if they received Vitamin D supplementation in last three months (half-life of Vitamin D- 6 to 8 weeks), were on glucocorticoids or antiepileptic drugs, had a history of chronic lung diseases, or their parents were not willing to give consent. The frequency and severity of previous episodes were recorded. For the purpose of the study, severity of wheezing was classified as Severe if any one of the following features were present, the child was classified as having severe wheezing:1) Need for hospitalization, 2) presence of wheezing at night time. 3) Need for nebulization 4) Need for oxygen support. Rest was classified as Non-severe. If the child was enrolled during admission, help of CASS scoring was also taken for severity determination(14). These patients were screened for Vitamin D levels using Electro-chemiluminescense-immunoassay (ECLIA). Controls were included from the vaccination clinic with proper consent.

Asthma predictive index (API) of patients was classified by written specific questionnaire. A 'positive' stringent API index requires recurrent episodes of wheezing (≥ 3 episodes/year) during the first 3 years of age (for loose index less than 3 episodes of wheezing can be included) and one of the two major criteria (Physician-diagnosed eczema or Parental asthma) or, two out of the three minor criteria (Physician-diagnosis allergic rhinitis, Wheezing without colds and Peripheral eosinophilia ≥ 4%). Two ml of EDTA blood was drawn for Vitamin D levels and eosinophil count.

Statistical analysis:

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used.

Statistical tests were applied as follows-

1. Quantitative variables were compared using Independent T test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups.
2. Qualitative variables were correlated using Chi-Square test/Fisher's Exact test. A p value of < 0.05 was considered statistically significant. Pearsons correlation coefficient was calculated to find the correlation between vitamin D levels and the number of API criteria fulfilled.

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

We enrolled 108 cases and 41 controls. The mean age of presentation was 2.18 ± 0.77 years for cases and 1.82 ± 0.62 years for controls. The youngest included child was one-year old. Children had fairly even distribution across various age groups; larger distribution was mainly in the age group between 2 years and 3 years. There was significant gender inequality in both the case and the control groups. There were 88 (81.4%) males and 20 (18.6%) females who fulfilled the criteria of recurrent wheezing. Among controls, there were 28 (68.3%) males and 13(31.7%) females. The male: female ratio of children with recurrent wheezing was 4.4:1. Among the study group 69 (63.8%) patients were from urban area and 39 (36.1%) of patients were from rural area. In the control group 34 (82.9%) were from urban area and 7 (17.1%) were from rural area. We calculated the serum levels of 25(OH) vitamin D of all the 108 cases and 41 controls. The mean levels of vitamin D in the cases and the controls were 16.08 ng/ml ± 14.9 and 23.37 ng/ml ± 17.9 respectively. The minimum and maximum levels of Vitamin D in the cases were 1.5 ng/ml and 36.75 ng/ml respectively. The minimum and maximum values in the controls group were 1.5 ng/ml and 70 ng/ml. The difference in vitamin D levels in the two groups was not statistically significant (p = 0.0619).

We further categorized the vitamin D levels of both the groups into deficient (< 20 ng/ml), insufficient (20–30 ng/ml) and sufficient (> 30 ng/ml). Among the cases 66 (61.1%) were deficient, 20 (18.5%) were insufficient, 22 (20.3%%) were sufficient. On the other hand, 24 (58.5%), 4 (9.8%) and 13 (31.7%) of the control population were deficient, insufficient and sufficient respectively.

In our study 91 (84%) cases were categorized as severe wheezers and 17 (16%) as non-severe. Among the Severe cases 57 (62.6%), 16 (17.5%) and 18 (19.7%) were vitamin D deficient, insufficient and sufficient respectively. In the non-severe group 9 (53%), 4 (23.5%) and 4 (23.5%) were vitamin D deficient, insufficient and sufficient respectively.

During enrolment, 13 cases showed features of pneumonia in chest Xray. We compared the vitamin D levels of these above children with the rest of the cases and found no statistically significant difference ($p = 0.949$ and likelihood ratio is .947).

We made an approximate estimate about exposure to sunlight. At least 15 min daily exposure was taken as adequate, although we didn't confirm the area of exposure and time of the day. In our study 39 (39%) cases and 12 (29.27%) controls gave history of at least 15 min daily exposure to sunlight. The difference in exposure to sunlight among the cases and controls was not significant ($p = 0.27$). In our study, we found no difference in the serum vitamin D levels between adequately and inadequately sun exposed children. ($p = 0.379$).

A weak negative correlation was found between the vitamin D levels and frequency of wheezing in the last one year($r=-0.118$), though not statistically significant ($p = 0.22$).

There was no significant difference in vitamin D levels between, urban and rural population ($p = 0.612$), among different socio-economic group ($p = 0.77$), vegetarians and non-vegetarians ($p = 0.6$).

We calculated the asthma predictive index of all our cases by specific pre-set questionnaires. In our study group 55 (51.0%) cases were API stringent index positive and 53 (49.0%) children were negative. The mean Vitamin D levels of API stringent Index positive and negative cases were 15.53 ± 10.52 ng/ml and 16.56 ± 11.9 ng/ml respectively.

Discussion

In this prospective observational study we aimed to examine the relationship between severities of wheezing and levels of serum vitamin D in toddlers. None of our cases or controls received prophylactic Vitamin D supplementation (400 IU/day) in contrast to children in developed countries. In this study, we found no difference in vitamin D levels between the recurrent wheezers and the normal children. However, both the groups had insuffient levels of vitamin D, suggestive of an endemic vitamin D deficiency in the general population. In humans, vitamin D is produced in the skin following exposure to ultraviolet B radiation (UVB) at the wave length ranging from 280–315 nm. Naturally occurring dietary sources of vitamin D are mainly non-vegetarian foods like meat, fish, eggs etc(15). Studies have shown that the UV radiation spectrum ideal for vitamin D synthesis (˜ 300 nm) in the skin also predisposes to tanning, DNA damage and skin cancer(16, 17). In our study, we made an approximate estimate about exposure to sunlight. A minimum of 15 min daily exposure was taken as adequate, although we didn't confirm the area of exposure and time of the day. In our study 66 (61.1%) cases and 29 (70.7%) controls gave history of at least 15 min daily exposure to sunlight. The difference in exposure to sunlight among the cases and

controls was not significant (p = 0.27). In our study, we found no difference in the serum vitamin D levels between adequately and inadequately exposed children. (p = 0.379). Thus, even perceived adequate sunlight exposure does not ensure adequate vitamin D levels, which makes a case for dietary supplementation of Vitamin D.

The male: female ratio of children with recurrent wheezing was 4.4:1 in or study. In our study, we got a high male: female ratio in contrast to some of the studies related to childhood asthma and wheezing carried out in other parts of India. A study on childhood asthma by Sharma et al in Jaipur, India showed a male: female ratio of 1.56:1(18). A study on prevalence of asthmatic children in New Delhi also showed almost similar distribution of male and female cases(19). Rosenthal M. explained the higher prevalence of asthma in young males by a combination of factors including small peripheral airway calibre before puberty, an increased prevalence of atopy and a higher prevalence of bronchial hyper reactivity(20).

The high male: female ratio found in our study could be partially attributed to the covert discriminatory behavioural practices which favour the treatment of sons over daughter especially in the states of Punjab and Haryana. A study from Government Medical College & Hospital, Chandigarh regarding gender related data on parameters like new OPD patients, revisit of patients in OPD, indoor admissions, utilization of vaccines; utilization of optional vaccines, babies who left against medical advice (LAMA) from neonatal nursery, revealed that the female patient population was significantly lower in all the above treatment sectors. But the female ratio was significantly more among the babies who left against medical advice (LAMA) from neonatal nursery(21). As per Indian Census 2011, despite having high literacy rate (86.05%), Chandigarh still has a low 0–6 years female sex ratio (845 females per 1000 males), which is much below the average national level (914 per 1000 males).

From different research studies as well as results from our study it is now clear that neither vitamin D rich diet nor adequate exposure to sunlight can protect from vitamin D deficiency. The only way to maintain sufficient blood vitamin D levels is vitamin D supplementations. Many developed countries like US and Canada are already using vitamin D fortified oils and milk products to ensure adequate vitamin D levels in their population(22). However, in India there is still no recommendation or government run program is initiated for universal vitamin D supplementation.

Conclusion

Our study showed that the overall prevalence of vitamin D deficiency is significantly high among Indian toddlers with recurrent wheezing. The mean levels of vitamin D was 16.08 ng/ml ± 14.9 in recurrent wheezers and 23.37 ng/ml ± 17.9 in normal children. We conclude that perceived adequate sunlight exposure cannot prevent vitamin D deficiency in Indian toddlers. A national programme for universal supplementation of vitamin D may help to control this rampant vitamin D deficiency. The Asthma Predictive Index of around 50% of the wheezers was positive, which warrants a more vigilant follow-up.

Declarations

1. **Funding:** Being a Government Institute, assay of Vitamin D levels and other tests were done free of cost. No other funds have been used for the study.
2. **Ethical Approval:** Ethical approval has been taken from Institutional Ethics Committee PGIMER, Chandigarh, before starting the research.
3. **Conflict of Interest:** On behalf of all authors, the corresponding author states that there is no conflict of interest.
4. **Informed Consent:** Informed consent has been taken from parents of all cases and controls before including them in the study.

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Tables

Table 1: Vitamin D levels in cases and controls

Vitamin D levels (ng/ml)	Cases (n=108)	Controls (n=41)	P Values	Odds ratio	(95% CI)
Deficient (< 20)	65 (60.2%)	24 (58.5%)	0.85	1.07	0.51-2.22
Insufficient(20-30)	20 (18.5%)	4 (9.8%)	0.20	2.1	0.67-6.57
Sufficient(>30)	23 (21.3%)	13 (31.7%)	0.20	0.58	0.76-1.3

Table 2: Vitamin D levels API stringent index positive and negative cases.

Vitamin D levels (ng/ml)	API Stringent index positive (n=55)	API stringent index negative (n=53)	P values
Deficient (< 20)	33 (60.0%)	32 (60.4%)	0.99
Insufficient (20-30)	12 (21.8%)	8 (15.1%)	0.46
Sufficient (>30)	10 (18.2%)	13 (24.5%)	0.48