

Vitamin A deficiency and wheezing

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Background: Vitamin A deficiency may increase the responsiveness of the respiratory tract and increase the risk of respiratory tract infection, resulting in airway obstruction and wheezing. This study aimed to investigate the relation between vitamin A deficiency and infant wheezing.

Methods: Three ml venous blood samples were collected from 331 hospitalized children who suffered from wheezing to determine the serum vitamin A concentration and the relationship between vitamin A and some causative factors of wheezing.

Results: The severity of vitamin A deficiency was related to the course of wheezing. In the persistent wheezing group, 14 patients (34.1%) were diagnosed as having severe vitamin A deficiency and 16 patients (39%) having moderate vitamin A deficiency; among the acute wheezing group, 18 patients (16.4%) were diagnosed as having severe vitamin A deficiency and 32 patients (29%) having moderate vitamin A deficiency. Comparison of the two groups revealed that there was a significantly higher rate of moderate and severe vitamin A deficiency in the persistent wheezing group than in the acute wheezing group ($P < 0.01$). The severity of vitamin A deficiency was related to the infants' wheezing severity. Severe vitamin A deficiency was found in 24 patients (47%) in the severe wheezing group and 8 (8%) in the mild and moderate wheezing groups. The rate of severe vitamin A deficiency was significantly higher in patients with severe wheezing than in those with mild and moderate wheezing ($P < 0.01$).

Conclusions: Serum vitamin A deficiency could be commonly found in infants with wheezing. The severity of vitamin A deficiency might be related to the course of wheezing and the infants' wheezing severity.

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Introduction

Vitamin A plays a key role in maintaining the integrity and consistency of skin and mucosal epithelial cells. It is closely related to the growth, proliferation and differentiation of tissues and cells and may participate in maintaining the regular immunologic function and internal environment stability in the human body. It may also have a protective role in preventing inflammatory changes of respiratory epithelium.^[1]

Vitamin A deficiency (VAD) is one of the four major nutritional deficiency diseases confirmed by World Health Organization (WHO). There were about 127 million preschool children who were affected and the global prevalence of VAD in children aged 0-4 years was about 21%.^[2,3] VAD appears to be a moderate public health problem in certain areas of China, and VAD rate was higher in low socioeconomic areas than in high socioeconomic areas.^[4] The latest survey indicated that VAD rate in children under 5 years old was 9.1% and the marginal deficiency rate of vitamin A was 41.8% in China.^[5]

VAD could reduce the ability of immune cells to fight off infection, and subsequently increase the risk of respiratory and digestive diseases in children. Infant wheezing is a common symptom and sign of VAD. It may be associated with breathing difficulty and cough, and may often lead to the parents seeking medical consultation. Wheezing can be a presenting feature of many conditions such as wheezy bronchitis, infantile asthma, viral induced wheezing, and bronchiolitis. Wheezing can be caused by virus infection and immature development of the lung and other uncertain factors. Vitamin A influences the development, maintenance, differentiation, and regeneration of lung epithelial cells and may play a central role in the development of airway diseases.^[6,7] It has been reported that VAD may increase the responsiveness of the respiratory tract, which is associated with exacerbation of asthma.^[8] All-trans retinoic acid can inhibit human

airway smooth muscle cells migration in response to platelet-derived growth factor and also inhibit platelet-derived growth factor which induced actin reorganization associated with migration.^[9] VAD was also reported to promote bronchial hyperreactivity in rats by altering muscarinic M2 receptor function.^[10,11]

This study was carried out to investigate the causal relationship of vitamin A deficiency and wheezing so as to provide evidences for potential prevention and treatment of infant wheezing.

Methods

Patients

A total of 331 hospitalized infants with wheezing were recruited in our study from the Respiratory Center, Children's Hospital Affiliated to Chongqing Medical University between November 2007 and February 2008, including 196 males and 135 females, with a female/male ratio of 1.45:1. They were aged 1 to 31 months with a mean of 11.6±8.5 months. The courses of wheezing ranged from 1 to 45 days with a mean time of 10.4±10.0 days. Diagnosis of wheezing was conformed to the clinical score system as follows.^[12] 1) Respiratory rate: 0: less than 30 breaths/min; 1 point: 31-45 breaths/min; 2 points: 46-60 breaths/min; 3 points: >60 breaths/min. 2) Wheezing: 0: none; 1 point: terminal expiratory or heard only with stethoscope; 2 points: entire expiration or audible on expiration without stethoscope; 3 points: inspiration and expiration without stethoscope. 3) Retractions: 0: none; 1 point: intercostal only; 2 points: tracheosternal; 3 points: severe with nasal flaring. 4) General condition: 0: normal; 3 points: irritable, lethargic, poor feeding. Based on the clinical total score, the disease severity can be divided into the following ranks: 0-4.9, mild wheezing; 5-8.9, moderate wheezing; and 9-12 points severe wheezing. Among the infants, 62 suffered from persistent wheezing (wheezing lasted for 4 or more weeks), and 269 from acute wheezing; 70 patients suffered from severe wheezing (oxygen saturation <94% in room air or significant respiratory distress with retraction, nasal flaring or requiring admission to intensive care) and 261 mild to moderate wheezing.

Vitamin A determination

Three ml venous blood samples were collected from the patients on admission. Serum retinol concentration was determined by using high-performance liquid chromatography (HPLC) following the method of Miller and Yang with slight modification.^[13] Blood was sampled into a dry tube and placed in a plastic box protected from sunlight. Serum was frozen at -20°C

until analysis. 200 µl serum was used for determining the serum vitamin A concentration with vitamin A measuring kit (Sigma, USA) following the protocol. The diagnostic criteria for vitamin A deficiency were established according to the national reference criteria recommended in 1995 in China: normal, vitamin A >1.05 µmol/L; suspected subclinical deficiency, 0.70-1.05 µmol/L; subclinical deficiency, <0.70 µmol/L; mild deficiency, 0.50-0.70 µmol/L; moderate deficiency, 0.35-0.50 µmol/L; severe deficiency, vitamin A <0.35 µmol/L.

Statistical analysis

The data were analyzed by SPSS11.5. They were expressed as means ± SD, and the enumeration data were compared with Chi-square test. $P < 0.05$ was considered statistically significant.

Results

Serum vitamin A concentrations

Among the 331 wheezing infants, normal serum vitamin A concentrations were found in 91 (27.5%) infants, and serum concentrations lower than 1.05 µmol/L were found in 240 patients (72.5%). Among them, 89 (26.9%) infants had suspected subclinical VAD, 71 (21.5%) had mild VAD, 48 (14.5%) had moderate VAD and 32 (9.7%) had severe VAD. All these patients had no clinical signs of VAD.

Vitamin A deficiency in infants at different ages

No statistical significance was found in serum vitamin A levels, rates of VAD and suspected VAD among different age groups ($\chi^2=5.38$, $P=0.49$). Serum vitamin A concentration <0.70 µmol/L was observed in 151 patients. No statistical significance was observed in VAD distribution between different ages ($\chi^2=7.32$, $P=0.29$).

Vitamin A deficiency and wheezing

In the 62 patients with persistent wheezing, 41 (66.1%) had various degrees of VAD. Among 269 with acute wheezing, various degrees of VAD were found in 110 patients (40.9%), much lower than those with persistent wheezing ($P < 0.01$). The results showed that moderate/severe VAD mainly occurred in patients who suffered from persistent wheezing, while mild VAD mainly occurred in patients with acute wheezing. Among the patients with persistent wheezing, 14 patients (34.1%) were diagnosed as having severe VAD and 16 (39%) having moderate VAD; in the acute wheezing group, 18 patients (16.4%) were diagnosed with severe VAD and 32 patients (29%) with moderate VAD (Table 1).

Table 1. Comparison between vitamin A deficiency and different courses of wheezing

wheezing course	n	Serum vitamin A concentration ($\mu\text{mol/L}$)		
		<0.35	0.35-0.50	0.50-0.70
Acute wheezing	110	18	32	60
Persistent wheezing	41	14	16	11
χ^2		10.26	10.41	9.98
P value		0.006	0.005	0.002
Total	151	32	48	71

Table 2. Relation between wheezing and vitamin A deficiency

Patient's condition	n	Serum vitamin A concentration ($\mu\text{mol/L}$)		
		<0.35	0.35-0.50	0.50-0.70
Mild wheezing	100	8	33	59
Severe wheezing	51	24	15	12
χ^2		33.49	33.01	30.28
P value		0.000	0.000	0.000
Total	151	32	48	71

Out of the 70 patients with severe wheezing, 51 (72.9%) were diagnosed with various degrees of VAD. However, in the 261 mild to moderate wheezing infants, 100 infants (38.3%) were diagnosed with VAD. The VAD rate was significantly higher in severe wheezing group than in mild to moderate wheezing group infants ($P < 0.01$). The rate of severe VAD was significantly higher in infants who suffered from severe wheezing than that in infants who suffered from mild and moderate wheezing ($P < 0.01$). Among the 32 infants who were diagnosed with severe VAD, 24 infants suffered from severe wheezing, accounting for 47% (24/51) of severe wheezing infants, which was remarkably higher than 8% (8/100) of infants who suffered from mild to moderate wheezing (Table 2).

Discussion

VAD remains an important problem in the developing world. There are about 0.25 billion children aged from 0 to 4 years who suffer from nutritional diseases of vitamin A in the world annually.^[3] A survey^[14] conducted in China in 2000 showed that the prevalence of subclinical VAD and suspected subclinical VAD was 11.7% and 39.2% respectively. Research conducted in 2006 indicated that VAD rate in children under 5 years old in China was declining.^[5] However, it was proved in our study that the prevalence of subclinical VAD was as high as 45.6% (151/331), and the prevalence of suspected subclinical VAD was as high as 26.9% (89 of 331) in patients with wheezing, which was much higher than that in normal children. Our finding indicates that the serum vitamin A level is even lower when patients

suffered from wheezing disease. Zhang et al^[15] reported that the prevalence of VAD was inversely related to ages, the prevalence of VAD decreased as the age of children increased and the severity of deficiency increased as the age decreased. However, our study did not reveal such a correlation between serum vitamin A levels and the age of wheezing infants, indicating that in China the correlation between VAD and infant age varies due to different areas and health conditions.

Our study revealed that serum vitamin A level was closely related to the course of wheezing. The prevalence of moderate and severe VAD was remarkably higher in patients with persistent wheezing compared to that in patients with acute wheezing. Normally, vitamin A is stocked in the liver, and it is transported to outer organism after the combination with retinol binding protein. The serum vitamin A level drops consequently as the vitamin A stockage in the liver decreased. Hence, the serum vitamin A level could act as a reflection of the vitamin A storage in liver.^[16] We suppose that patients with persistent wheezing demand more vitamin A to restore the impaired tracheobronchial epithelium than patients with acute wheezing. While the intake of vitamin A during the course of disease decreases, the level of retinol binding protein decreases during the inflammation period. The consumption of antioxidant may be increased significantly by the increased level of oxyradical resulting from inflammation and infection, which leads to a more significant decline in serum vitamin A in patients who suffer from persistent wheezing. Low vitamin A status may result in greater bacterial adherence and colonization and therefore may increase the risk of bacterial infection and prolong the disease course.^[17] The renovation ability of the immune system and respiratory tract epithelium might be damaged in a serum vitamin A level of 1.05 $\mu\text{mol/L}$ or less.^[8,18] Lack of vitamin A might also cause decreased proliferation and squamous metaplasia and decreased defensive ability of glandular cells, which might increase the risk of complications such as respiratory infection and airway obstruction in basal cells and mucous cells due to the lack of vitamin A.^[19] These two factors interact with each other, and the course of wheezing may be prolonged and the vitamin A level may be reduced.

Vitamin A plays a significant role in the differentiation and integrity maintenance of the respiratory tract epithelial cells. Retinoic acid may reduce eosinophilic airway inflammation, one of the prominent pathological features of bronchial asthma^[19] and inhibit human airway smooth muscle cells migration.^[9] The deficiency of vitamin A causes cilia disappear in ciliated columnar epithelial cells of the respiratory tract, accompanied by squamous

metaplasia and decreased defensive ability of glandular cells. The bacteria might invade the human body, causing secondary respiratory infection,^[20] or even hyperreactivity in the airway,^[9] finally resulting in wheezing. The correlation between the severity of pneumonia and retinol level has not been reported according to the studies available.^[21] WHO has also put emphasis on the role of severe infectious diseases in acute VAD.^[22] We found that the prevalence of severe VAD in patients with severe wheezing was much higher than that in the non-severe group, indicating that the level of vitamin A might be associated with the severity of wheezing. However, the causal relation between these two was not elucidated: whether severe VAD causes critical wheezing or critical wheezing promotes severe VAD.

In short, the current study shows that there is a high prevalence of VAD in wheezing patients in Chongqing, which does not vary with ages. But the degrees of VAD may be related to the course and severity of wheezing.

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Ethical approval: The study was approved by the Ethics and Human Research Committees of the Children's Hospital, Chongqing Medical University.

Competing interest: None declared.

Contributors: Luo ZX and Liu EM proposed the project and Luo ZX wrote the paper. Luo ZX is the guarantor.

References

- Morabia A, Menkes MJ, Comstock GW, Tockman MS. Serum retinol and airway obstruction. *Am J Epidemiol* 1990;132:77-82.
- West KP Jr. Extent of vitamin A deficiency among preschool children and women of reproductive age. *J Nutr* 2002;132(9 Suppl):2857S-2866S.
- Guilbert JJ. The world health report 2002—reducing risks, promoting healthy life. *Educ Health (Abingdon)* 2003;16:230.
- Jiang JX, Lin LM, Lian GL, Greiner T. Vitamin A deficiency and child feeding in Beijing and Guizhou, China. *World J Pediatr* 2008;4:20-25.
- Zhao L, Yu D, Liu A, Jia F. Analysis of health selective survey result of children and pregnant/Lying-in women in China in 2006. *Wei Sheng Yan Jiu* 2008;37:65-67. [In Chinese]
- Chytil F. The lungs and vitamin A. *Am J Physiol* 1992;262(5 Pt 1):L517-527.
- Gray T, Koo JS, Nettesheim P. Regulation of mucous differentiation and mucin gene expression in the tracheobronchial epithelium. *Toxicology* 2001;160:35-46.
- Biesalski HK, Nohr D. Importance of vitamin A for lung function and development. *Mol Aspects Med* 2003;24:431-440.
- Day RM, Lee YH, Park AM, Suzuki YJ. Retinoic acid inhibits airway smooth muscle cell migration. *Am J Respir Cell Mol Biol* 2006;34:695-703.
- McGowan SE, Smith J, Holmes AJ, Smith LA, Businga TR, Madsen MT, et al. Vitamin A deficiency promotes bronchial hyperreactivity in rats by altering muscarinic M(2) receptor function. *Am J Physiol Lung Cell Mol Physiol* 2002;282:L1031-L1039.
- McGowan SE. Vitamin A deficiency increases airway resistance following C-fiber stimulation. *Respir Physiol Neurobiol* 2007;157:281-289.
- Wang EE, Milner RA, Navas L, Maj H. Observer agreement for respiratory signs and oximetry in infants hospitalized with lower respiratory infections. *Am Rev Respir Dis* 1992;145:106-109.
- Miller KW, Yang CS. An isocratic high-performance liquid chromatography method for the simultaneous analysis of plasma retinol, alpha-tocopherol, and various carotenoids. *Anal Biochem* 1985;145:21-26.
- Tan ZW. Survey on serum vitamin A levels among 0-6 years children of China. *Chin J Child Health Care* 2002;10:303-306.
- Zhang YK, Yuan WX, Li ZQ. Survey on Vitamin A deficiency in children under 6-years in Hebei Province. *Matern Child Health Care China* 2007;22:4549-4550. [In Chinese]
- Stephensen CB, Franchi LM, Hernandez H, Campos M, Colarossi A, Gilman RH, et al. Assessment of vitamin A status with the relative-dose-response test in Peruvian children recovering from pneumonia. *Am J Clin Nutr* 2002;76:1351-1357.
- Chandra RK. Increased bacterial binding to respiratory epithelial cells in vitamin A deficiency. *BMJ* 1988;297:834-835.
- Stephensen CB. Vitamin A, infection, and immune function. *Annu Rev Nutr* 2001;21:167-192.
- Takamura K, Nasuhara Y, Kobayashi M, Betsuyaku T, Tanino Y, Kinoshita I, et al. Retinoic acid inhibits interleukin-4-induced eotaxin production in a human bronchial epithelial cell line. *Am J Physiol Lung Cell Mol Physiol* 2004;286:L777-L785.
- Reyes H, Villalpando S, Pérez-Cuevas R, Rodríguez L, Pérez-Cuevas M, Montalvo I, et al. Frequency and determinants of vitamin A deficiency in children under 5 years of age with pneumonia. *Arch Med Res* 2002;33:180-185.
- Da Silva R, Lopes E Jr, Sarni RO, Taddei JA. Plasma vitamin A levels in deprived children with pneumonia during the acute phase and after recovery. *J Pediatr (Rio J)* 2005;81:162-168.
- García-Casal MN, Layrisse M. Dietary iron absorption. Role of vitamin A. *Arch Latinoam Nutr* 1998;48:191-196.

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