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.

Key words: infant; vitamin A deficiency; wheezing

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 Heath 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.\(^8\) 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 expiration 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).

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

<table>
<thead>
<tr>
<th>Patient's condition</th>
<th>Serum vitamin A concentration (μmol/L)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.35</td>
<td>0.35-0.50</td>
</tr>
<tr>
<td>Acute wheezing</td>
<td>110</td>
<td>18</td>
</tr>
<tr>
<td>Persistent wheezing</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>χ²</td>
<td>10.26</td>
<td>10.41</td>
</tr>
<tr>
<td>P value</td>
<td>0.006</td>
<td>0.005</td>
</tr>
<tr>
<td>Total</td>
<td>151</td>
<td>32</td>
</tr>
</tbody>
</table>

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. A survey 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 μmol/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.[8] 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, or even hyperreactivity in the airway, finally resulting in wheezing. The correlation between the severity of pneumonia and retinol level has not been reported according to the studies available. WHO has also put emphasis on the role of severe infectious diseases in acute VAD. 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 level of vitamin A might be associated with the severity of wheezing.

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Competing interest: None declared.

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

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