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Plasma vitamin C (ascorbic acid) levels in asthmatic children

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Summary

Plasma concentration of ascorbic acid was determined in fifty-one asthmatic children and a group of matched controls. The mean ascorbic acid level of 0.54 mg/100 ml among the asthmatics was significantly lower than a mean of 0.84 mg/100 ml for controls ($P < 0.001$). Ascorbic acid level was directly related to the socio-economic class (SC) since asthmatic children from SC I, II and III had significantly higher ascorbic acid levels than those from SC IV and V. There was however, no relationship between the plasma ascorbic acid level and atopy, frequency of asthmatic attacks over the previous 12 months and the duration of asthma. It is postulated that if plasma ascorbic acid level was related to the susceptibility to viral respiratory tract infections, the observed low level of the vitamin in the asthmatics would make them more liable to such infections which are capable of precipitating acute asthmatic attacks. Confirmation of our results would indicate the need for regular ascorbic acid supplement in some children with bronchial asthma.

Résumé

Dans cette étude, la concentration plasmatique de l'acide ascorbique (AA) a été évaluée chez cinquante-et-un enfants asthmatiques et dans un groupe contrôle équivalent. La valeur moyenne de 0.54/100 ml chez les asthmatiques était plus basse que celle des contrôles (0.84 mg/100 ml) de façon significative ($P < 0.001$) le taux de l'AA était directement lié au niveau socio économique (NCS) puisque les enfants

asthmatiques du NSC I, II, III avait des valeurs statistiquement supérieures à celles des enfants du NSC IV et V. Aucune relation n'a été démontrée entre les taux plasmatiques de l'AA et l'atopie, la fréquence des crises asthmatiques au cours des 12 mois précédents et la durée de l'asthme. Nous postulons donc que si la valeur plasmatique de l'AA était liée à la susceptibilité aux infections des voies respiratoires d'origine virale les faibles taux de la vitamine chez les asthmatiques les rendraient plus disposés à de telles infections capable de précipiter des crises asthmatiques aiguës. La confirmation de nos résultats suggérerait le besoin d'un apport régulier de l'AA chez certains enfants souffrant de l'asthme bronchique.

Introduction

Ascorbic acid (vitamin C) is considered by some workers (Coulehan *et al.*, 1974; Wilson, 1974) to be a useful agent in the prophylaxis and management of viral upper respiratory tract infections (URTI), while others (Walker *et al.*, 1967) hold contrary views. Reports have shown that some acute attacks of asthma are precipitated by viral URTI (McIntosh, *et al.*, 1973; Mitchell, Inglis & Simpson, 1976). The more frequent such infections in asthmatics, the more frequent will be the likelihood of acute attacks. If the plasma ascorbic acid level were related to the susceptibility to URTI, in which destruction of respiratory mucous membrane takes place as it does in atopic allergy (Priest, 1970), then it is possible that such levels might not only be lower in asthmatics than in healthy children, but it may also be related to the

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frequency of acute attacks of asthma in the former. In order to test this hypothesis, we have determined the plasma levels of vitamin C in asthmatic children and in controls.

Materials and methods

The subjects consisted of fifty-one consecutive asthmatic children (twenty-eight males; twenty-three females) aged 2–16 years, who had no obvious clinical evidence of URTI when they were seen during a period of 5 months at the Asthma Clinic, Department of Paediatrics, University College Hospital (UCH), Ibadan. The diagnostic criteria of asthma have been published elsewhere (Aderole & Oduwole, 1983). The grading of severity of asthma, which was based on the frequency of acute attacks, was modified from an earlier one (Aderole, 1979). Patients who had had an average of less than one attack per month during the previous 12 months were graded as mild, while those whose attacks averaged one or more per month, were regarded as having severe asthma. Forty-three (84%) of the fifty-one subjects had no clinical evidence of bronchial obstruction at the time of the study. The remaining eight (16%) were not in acute attacks, although they had residual airways obstruction as manifested by the presence of pulmonary rhonchi. The controls consisted of apparently healthy children matched for age, sex and socio-economic background with the subjects. Socio-economic stratification was based on the paternal occupation (Aderole, 1981). The controls were not subject to unduly frequent attacks of URTI, neither was any of them suffering from *coryza* or any other inter-current infection at the time of the study. Informed consent was obtained from the parents of both asthmatics and controls.

Dietary and drug history obtained for each child showed that the major items of food in virtually all the cases consisted of rice, 'amala', 'eba', yams, bread, 'pap' and 'eko' ('amala' is a meal prepared from yam flour, eba from cassava flour while 'pap' and 'eko' are prepared from maize flour). Other items taken occasionally by a few, particularly those from the higher socio-economic classes included milk, egg, carrots, porridge and salad. With regard to drinks and beverages, the majority of the children

drank soft drinks such as 'Coca-Cola', 'Fanta' and 'Sprite' occasionally, while thirty-three each of asthmatics and controls, drank tea or chocolate ('Bournvita') fairly regularly. Popular fruits eaten by sizeable proportions of both asthmatics and controls included oranges, mangoes and pineapple. Most of the asthmatics were on intermittent bronchodilator therapy consisting mainly of salbutamol ('Ventolin'), 'Franol' and 'Tedral', supplemented by various cough suppressants/expectorants such as 'Tussifin' and 'Benylin'. Twenty-six (51%) asthmatics were apparently on irregular multivitamin supplement while two admitted to taking ascorbic acid in addition, for acute attacks presumed to be precipitated by URTI. Similarly, twenty-two (43%) of the fifty-one controls were receiving irregular multivite supplements.

Asthma was mild in thirty-four (67%) of the fifty-one cases and severe in the remaining seventeen (33%). Asthma had lasted for 1–15 years (mean, 6.1 ± 3.83) in the males, and 1.5–11 years (mean, 6.15 ± 3.02) in the females. The interval between the study and last asthmatic attack varied between 1 day and 2 years.

Nutritional state based on skinfold thickness, weight and general appearance was adjudged to be fair to excellent in fifty of the fifty-one asthmatics, while the remaining child was considered to be malnourished; he had a weight that was below the Oje mean weight minus 2 standard deviations for his age and sex (Janes, 1974). By comparison, forty-nine of the fifty-one controls were well nourished while the remaining two were underweight.

Five ml of venous blood, obtained from each child, was placed in a heparinized tube and centrifuged. Plasma obtained after centrifugation was assayed immediately for ascorbic acid (Varley, 1969). Skin sensitivity tests by the prick method were carried out as previously described (Aderole & Oduwole, 1981).

Statistical analysis was carried out using the Students *t* and chi-squared tests.

Results

Plasma Vitamin C levels

Table 1 summarizes the mean plasma ascorbic

Table 1. Plasma vitamin C levels in asthmatics and controls

	Males			Females			All		
	No. of cases	Mean (mg/100 ml)	s.d.	No. of cases	Mean (mg/100 ml)	s.d.	No. of cases	Mean (mg/100 ml)	s.d.
*Asthmatics	28	0.51	0.12	23	0.56	0.16	51	0.54	0.15
†Controls	28	0.85	0.28	23	0.83	0.30	51	0.84	0.28

s.d. = Standard deviation.

*M v F: $t = 1.000$ on 49 d.f.; $P > 0.1$.

†M v F: $t = 0.2500$ on 49 d.f.; $P > 0.5$.

Asthmatics v. controls (males): $t = 5.5000$ on 54 d.f.; $P < 0.001$.

Asthmatics v. controls (females): $t = 3.8571$ on 44 d.f.; $P < 0.001$.

Asthmatics v. controls (both sexes): $t = 7.5000$ on 100 d.f.; $P < 0.001$.

v. = compared with.

acid levels in asthmatics and controls. There were no significant sex differences in the levels in both asthmatics and controls. However, the mean ascorbic acid levels in asthmatics were significantly lower than the corresponding levels in the controls ($P < 0.001$).

The highest plasma vitamin C level recorded in the asthmatics was 1.09 mg/100 ml in a 10 year old girl with mild asthma of 9 years duration, from social class III, whose last attack was over 6 months before the study. She was well nourished, took multivite supplements occasionally and had a negative skin test. Conversely, the lowest vitamin C level of 0.38 mg/100 ml in the asthmatics was in a 3 year old male asthmatic of 2 years duration from SC IV. He was of good nutritional status and his last acute asthmatic attack was 3 months before the study. He was not in the habit of taking vitamin supplements.

Vitamin C and severity of asthma

The mean vitamin C level (0.54 ± 0.15 mg/100 ml) in those with mild asthma was similar to the mean level in those with severe asthma (0.54 ± 0.14 mg/100 ml) ($P > 0.5$) (Table 2). There was no significant difference in the distribution of the social classes and ages between those with mild and others with severe asthma.

Vitamin C and duration of asthma

The mean vitamin C level in twenty-three asthmatics whose disease had lasted for less than 5 years was 0.5 ± 0.11 mg/100 ml and was similar to 0.56 ± 0.17 mg/100 ml in the remaining twenty-eight whose asthma had lasted for over 5 years ($P > 0.1$).

Skin sensitivity tests and Vitamin C levels

Twenty-one (66%) of thirty-three asthmatics were apparently atopic as shown by their positive reactions on skin sensitivity testing. The mean vitamin C level in those with positive tests was 0.53 ± 0.12 mg/100 ml compared with 0.58 ± 0.22 mg/100 ml in those with negative reactions ($P > 0.1$).

Vitamin C levels and ingestion of vitamin supplements

The mean vitamin C level in twenty-six asthmatics who were reported to be taking vitamin supplements irregularly was, at 0.56 ± 0.17 mg/100 ml, not significantly higher than 0.51 ± 0.10 mg/100 ml in the remaining twenty-five who were not in the habit of taking such supplements ($P > 0.1$). Among the twenty-six subjects who took multivite, there were two

Table 2. Plasma vitamin C levels and severity of asthma

Attack	No. of cases	Mean (mg/100 ml)	Standard deviation	<i>P</i>
Mild	34	0.54	0.15	> 0.5
Severe	17	0.54	0.14	

who, in addition, took vitamin C for colds. They were both mild cases, one male and the other female, each aged 9 years, from SC I and SC III, respectively. Vitamin C levels in these two were 0.7 and 0.53 mg/100 ml, respectively. Similarly, the mean vitamin C level in the twenty-two controls who received multivite supplements (0.9 ± 0.27 mg/100 ml) was not significantly different from 0.8 ± 0.29 mg/100 ml in the twenty-nine who did not.

Vitamin C and social class

As shown in Table 3, while the mean vitamin C levels were not significantly related to the social classes among the controls, those from social classes I/II, nevertheless had the highest mean values. In the asthmatics, those from SC I/II and III had similar mean levels which were however, significantly higher than the mean level in those from SC IV/V ($P < 0.02$; $P < 0.01$, respectively).

Discussion

Normal values for plasma ascorbic acid in children have been established in some parts of the world (Bell, Davidson & Scarborough, 1961; Eastham, 1971), but not in Nigeria. This lack of normal values prompted the comparison of ascorbic acid levels in the asthmatics with those in the controls from similar socio-economic background.

The present finding that plasma ascorbic acid levels were significantly lower in our asthmatic subjects of both sexes than in controls has some clinical implications and appears not to have been reported previously. The normal physiologic functions of ascorbic acid are to maintain tissue defence mechanism and integrity and enable tissue replacement and healing to take place (Wilson, 1974). Since destruction of respiratory mucous membrane takes place in both the common cold and atopic allergy (Priest, 1970), a reduction in the tissue concentration of ascorbic acid would probably

Table 3. Plasma vitamin C levels and socio-economic class

Socio-economic class*	Asthmatics			Controls		
	No. of cases	Mean (mg/100 ml)	s.d.	No. of cases	Mean (mg/100 ml)	s.d.
I + II	9	0.60	0.16	8	0.93	0.4
III	26	0.57	0.17	27	0.81	0.31
IV + V	16	0.46	0.04	16	0.85	0.16

*Aderere (1981).

s.d. = Standard deviation.

S/C = Socio-economic class.

For asthmatics: S/C I + II v. S/C III $P > 0.5$; S/C I + II v. S/C IV + V $P < 0.02$; S/C III v. S/C IV + V $P < 0.01$.

For controls: S/C I + II v. S/C III $P > 0.1$; S/C I + II v. S/C IV + V $P > 0.5$; S/C III v. S/C IV + V $P > 0.5$.

v. = compared with.

delay the healing of such mucous membrane surfaces. Such deficiency is likely to prolong the symptoms due to the injured mucosa. If the comparative levels of plasma ascorbic acid obtained in asthmatics and controls in the present study were a true reflection of the tissue levels of the vitamin, the lower levels in the asthmatics would represent a relative deficient state which may result in the prolongation of symptoms during acute attacks when there is injury to the mucous membrane. Similarly, if it is true, as claimed by some workers (Coulehan *et al.*, 1974; Wilson, 1974) that ascorbic acid protects against infection of the respiratory tract by viruses, the low level of the vitamin observed in the asthmatics is likely to make them more vulnerable to such infection. This in turn, would tend to result in an increased frequency of acute asthmatic attacks.

Evidence that ascorbic acid is important in the maintenance of pulmonary function has been reported by McNally (1953) who showed that the administration of ascorbic acid caused pulmonary dilation and that urinary excretion of the vitamin during acute episodes of asthma was significantly reduced and increased again when the wheezing disappeared. This would suggest that during these episodes, ascorbic acid was being actively metabolized probably at the bronchial mucosal surface, thus resulting in the depletion of the plasma ascorbic acid content to levels below the renal threshold. In a recent study of the relationship between ascorbic acid and pulmonary function, Schachter and Schlesinger (1982) showed that pretreatment with ascorbic acid led to a significant attenuation of bronchospasm in asthmatics with exercise-induced bronchospasm. Another possible mode of action of ascorbic acid on the respiratory tract in bronchial asthma may be inferred from the report by Bell *et al.* (1961), that in the scorbutic guinea pig, the arterioles appeared to be less sensitive to the injection of adrenaline than those of normal animal. If this phenomenon should also occur in man's bronchi which contain smooth muscle like the arterioles and normally dilates in response to adrenaline, then it may be postulated that ascorbic acid deficiency in asthmatics is likely to make acute bronchospasm relatively insensitive to adrenaline and other sympathomimetic bronchodilators. Thus, the actions of vitamin C in bronchial asthma may be two-fold; first the

prevention of acute attacks precipitated by viral colds and secondly, an early reversal of bronchospasm once an attack is established. If the results obtained in the present study are confirmed in larger series and elsewhere, there may be a case for routine administration of ascorbic acid to asthmatic children in an effort to reduce the frequency and thus the severity of their attacks. In addition, the administration of high doses of the vitamin during acute attacks may hasten recovery.

Our observation that ascorbic acid level was related to the socio-economic background of the patients is similar to that by Smithells, Sheppard and Schorah (1976) who reported significantly higher ascorbic acid levels in patients from SC I and II than in those from the other classes. This observed relationship is likely to be due to the easier access to and therefore, a probable higher intake of ascorbic acid containing fruits by children from the upper social classes. Although, according to the dietary history obtained in the present study, there was no appreciable difference in the types of food and fruits taken by children from the various socio-economic groups, the quantities of such items were probably different.

That the ascorbic acid levels were not related to the frequency of asthmatic attacks in the present study suggest that any severe ascorbic acid deficiency present in the asthmatics was only transient and had been corrected by the time the blood specimens were obtained or that the reporting of the frequency of acute attacks during the previous 12 months by the parents was inaccurate. Alternatively, perhaps most of such attacks were not precipitated by the common cold or other viral URTI.

Further research to determine the ascorbic acid levels during acute attacks of asthma and the correlation of these levels with the isolation of viruses from the respiratory tract is deemed necessary. It might also be rewarding to undertake therapeutic trials with parenteral ascorbic acid during acute asthmatic attacks and on long-term regular basis in these children.

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