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Iron status and its relation to lung function in pediatric asthmatics: a cross-sectional study

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Abstract

Background: Asthma and iron deficiency are common pediatric conditions. In addition, iron deficiency may affect spirometry results in asthmatic children. So, we aimed to assess the effect of ion status on lung function in childhood asthma.

Results: In this cross-sectional study, fifty asthmatic pediatric patients aged from 6 to 16 years presented to our institute during the period from (June 2018 to December 2018) were enrolled. Asthmatic patients were classified according to their complete blood count and iron profile into 2 groups: group 1, asthmatic children without iron deficiency anemia (IDA); and group 2, asthmatic children with IDA. All patients underwent full history taking, clinical examination, laboratory investigations, asthma control test, and pulmonary function tests (PFTs). The study showed that PFTs' parameters (forced expiratory volume in one second (FEV1) % of predicted, FEV1/forced vital capacity, and maximal mid expiratory flow (MMEF) 25–75% of predicted) were significantly lower among asthmatics with IDA (80.62 ± 18.13, 78.36 ± 11.22, 62.35 ± 26.67) than among asthmatics without IDA (93.45 ± 15.51, 87.68 ± 10.81, 82.10 ± 24.74), respectively (p =0.012, 0.006, 0.012). Also, poorly controlled asthma was significantly higher among asthmatics with IDA (p =0.001). In addition, there was a statistically significant positive correlation between forced spirometry parameters, hemoglobin, and ferritin level (p=0.012, 0.042). Moreover, there was a significant positive correlation between hemoglobin level and MMEF 25–75% of predicted (p=0.012).

Conclusions: Lower iron status negatively affects the lung function in asthmatic children with a more obstructive pattern among asthmatics with IDA.

Keywords: Childhood asthma, Iron deficiency anemia, Asthma control test, FEV1, Lung function

Background

Asthma is a wide public health problem affecting 8.4% of children [1]. Its incidence increased worldwide [2]. Pathophysiologic occasions creating asthma, including inflammation, upsurges in Th2 cells, and muscle tightening, can associate with iron obtainability [3, 4].

Preservation of iron homeostasis is of extreme importance for the respiratory physiology and pathophysiology where local iron deficit may result in certain respiratory function impairment of forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, and peak expiratory flow [5]. Therefore, the objective of the current study was to evaluate the impact of iron status on the results of pulmonary function tests among asthmatic children.

Materials and methods

Study design and setting

This cross-sectional study was carried out on fifty asthmatic children in the age group of 6–16 years who were attending our institute during the period from (June 2018 to December 2018). The study was registered at https://www.clinicaltrials.gov/ (ID: NCT05277610).

The study was approved by the Ethics Research Committee of the Faculty of Medicine, Ain Shams University.

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All patients were invited to participate, and informed consents were obtained from their parents or guardians and children older than 7 years prior to inclusion in the study.

Study subjects

Inclusion criteria

A. Confirmed diagnosis of bronchial asthma: The diagnosis of bronchial asthma in the studied children was based on clinical examination and applying the following criteria mentioned in previous studies [6, 7]:

   1. History of recurrent or chronic symptoms characteristic of asthma (more than three episodes were present).
   2. The findings on physical check of distinctive musical wheezing (present in relationship with signs and absent with signs' resolution).
   3. The demonstration of variable expiratory airflow limitation by spirometry (a post-bronchodilator increase in FEV1 of >12%) [8].
   4. Exclusion of alternative diagnoses

B. The diagnosis of iron deficiency anemia was supported by criteria provided and updated by World Health Organization [9, 10].

Exclusion criteria

A) Chronic lung diseases other than asthma; (B) any known hematological disorders like thalassemia or any other type of anemia other than IDA; (C) severe systemic illness as liver, renal diseases, and nutritional disorders; (D) congenital malformations of the chest wall; (E) wheezes for the first time, and (F) if the patients were taking any iron supplementation at the time of the study or in the previous 3 months prior to the study.

Study methods

For each child, a detailed medical history was obtained including the personal history, history of present illness including intermittent or recurrent symptoms of cough, shortness of breath, wheezes, dyspnea, chest tightness and pallor, history of allergy and exposure to precipitating factors, nutritional history, history of passive smoking, and family history of atopy.

In addition, all children included in the study were subjected to a thorough clinical examination with a special stress on chest examination including signs of tachypnea, hyperinflated chest, hype-resonance on percussion, signs of respiratory distress, prolonged expiratory period, and expiratory rhonchi on chest auscultation, along with the anthropometric measurements including body mass index (BMI) which was calculated using the following formula: BMI=weight/height^2 in meter square. Chest X-ray was done to exclude other causes of wheezes rather than asthma. Furthermore, complete blood count (CBC), iron profile (Serum iron, serum total iron binding capacity (TIBC), serum ferritin, and transferrin saturation) were reviewed from the patients' records in the previous month. Asthma control level was measured for all the studied patients by the Global Initiative for Asthma (GINA) criteria [11], and the Asthma Control Test (ACT) [12], ACT consists of five items. It has been applied for asthmatic patients from the age of 12 years evaluating the preceding 4 weeks and a seven-item childhood ACT (C-ACT) which has been used in asthmatic children aged 4–11 years [13]. A score cut-off point of 19 indicated uncontrolled asthma for both questionnaires. Additionally, pulmonary function tests (PFTs) were performed for cooperative children older than 6 years with average mentality.

Study procedure

Pulmonary function testing was performed using standardized spirometry. It was done for asthmatic patients using (JAEGER apparatus, Care Fusion Germany, 2011). Lung function was measured by forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, and maximal mid-expiratory flow (MMEF 25–75%) of FVC. Each was measured 3 times, and the best effort was recorded. All of FEV1, FVC, and MMEF 75/25 measurements are reported as percent of predicted values for age, height, and sex. All pulmonary function tests were performed and interpreted according to the American Thoracic Society Guidelines (ATS)/European Respiratory Society (ERS) standards [14, 15].

Statistical analysis

The results were statistically analyzed using the statistical package for social sciences, version 20.0 using (SPSS Inc., Chicago, Illinois, USA [16]. Numerical variables were reported in terms of mean and standard deviations (SD). Categorized variables were reported in terms of numbers (n) and percentages (%). The baseline characteristics of asthmatic children with or without anemia were compared using unpaired "Student's" *t* test and chi-square tests for parametric and non-parametric parameters. Correlations between various variables were done using Pearson correlation equation for linear relation in normally distributed variables. The *P* value less than 0.05 was considered to be statistically significant.

Sample size calculation

The sample size was calculated using PASS 11.0 and was based on a study carried out by AlKhateeb et al. [17]. Group sample sizes of at least 17 patients in group 1 (asthmatic patients without iron deficiency anemia) and 17 patients in group 2 (asthmatic patients with iron deficiency anemia) achieve 81% power to detect a difference of −9.1 between the null hypothesis that both group means are 52.3 and the alternative hypothesis that the mean of group 1 is 61.4 with the estimated group standard deviations of 10.0 and 8.0 and with a significance level (alpha) of 0.05000 using a two-sided two-sample *t* test. The primary outcome variable is FEV1/FVC. The sample size calculation was based on comparisons between two means.

Results

The study included fifty children diagnosed as bronchial asthma. According to their hemoglobin levels and iron profile, asthmatic patients were divided into two groups: group 1, asthmatic children without IDA (66%) (n=33); and group 2, asthmatic children with IDA (34%) (n=17).

No statistically significant differences regarding the demographic and anthropometric data were observed between asthmatic patients with and without IDA (p>0.05) (data not shown).

Pulmonary function test parameters among the studied patients

As shown in Table 1, there was a statistically significant difference between group 1 and group 2 concerning respiratory function limitations in (FEV1% of predicted, FEV1/FVC, MMEF 25–75% of predicted) which were superior in group 2 (asthmatics with IDA) (52.9%), (58.8%), and (53%), than in group 1 (asthmatics without IDA) (18.2%), (15.2%), and (12.1%), respectively, which denoted that anemic asthmatics had more pronounced deterioration of lung function on spirometry study than those with asthma alone (p value =0.011, 0.019, and 0.018), respectively.

The pulmonary function tests' results in relation to IDA

There was a statistically significant difference between group 1 and group 2 regarding the pulmonary function test results where moderate to moderately severe obstructive pattern was significantly higher in group 2 (35.2%) than group 1 (9.1%), denoting a more severe airway disease among asthmatics with IDA (p = 0.032), as shown in Table 2.

Asthma control level and iron status

As displayed in Table 3, there mean C-ACT score was significantly lower among asthmatics with IDA (15.29 ± 2.46) than those without IDA (20.04 ± 2.32), (p value < 0.001). In addition, very poorly controlled asthma was significantly more prevalent among the

Table 1 Comparison between groups 1 and 2 regarding pulmonary function test parameters

Pulmonary function test parameters		Asthmatics without IDA Group 1 *(n=33)*	Asthmatics with IDA Group 2 *n=17)*	*p* value
FEV1[a]% of predicted	Mean ± SD	93.45 ± 15.51	80.62 ± 18.13	0.012*
	Range	58–125.7	57–112.6	
FVC of % predicted	Mean ± SD	95.92 ± 12.58	93.18 ± 12.31	0.467
	Range	75.1–124	80–125.2	
FEV1/FVC	Mean ± SD	87.68 ± 10.81	78.36 ± 11.22	0.006**
	Range	58–113.9	54–96	
MMEF 25–75% of predicted	Mean ± SD	82.10 ± 24.74	62.35 ± 26.67	0.012*
	Range	19.3–132.8	16–105	
FEV1 % of predicted interpretation	Normal	27 (81.8%)	8 (47.1%)	0.011*
	Decreased	6 (18.2%)	9 (52.9%)	
FVC of % predicted interpretation	Normal	31 (93.9%)	17 (100.0%)	0.300
	Decreased	2 (6.1%)	0 (0.0%)	
FEV1/FVC interpretation	Normal	28 (84.8%)	7 (41.2 %)	0.019*
	Decreased	5 (15.2%)	10 (58.8 %)	
MMEF 25-75% of predicted interpretation	Normal	29 (87.9%)	8 (47%)	0.018*
	Decreased	4 (12.1%)	9 (53%)	

**p value <0.05 significant*; ***p* value< 0.01, highly significant; *IDA*, iron deficiency anaemia; *FEV1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *MMEF*, maximal mid-expiratory flow

Table 2 Comparison between asthmatics without IDA and asthmatics with IDA according to the pulmonary function test results

Pulmonary function test results interpretation	Asthmatics without IDA Group A *(n=33)*	Asthmatics with IDA Group B *(n=17)*	*p* value
Normal pulmonary function test	27 (81.8%)	7 (41.2%)	0.032*
Restrictive airway disease	1 (3.0%)	0 (0.0%)	
Mild obstructive airway disease	2 (6.1%)	4 (23.5%)	
Moderate obstructive airway disease	1 (3.0%)	3 (17.6%)	
Moderately severe obstructive airway disease	2 (6.1%)	3 (17.6%)	

**p value <0.05 significant*

Table 3 Comparison between asthmatics without IDA and asthmatics with IDA according to the asthma control test

Asthma control test (ACT)		Asthmatics without IDA Group A *(n=33)*	Asthmatics with IDA Group B *(n=17)*	*P* value
Childhood asthma control test ($n = 39$)	Mean ±SD	20.04 ± 2.32	15.29 ± 2.46	< 0.001**
	Range	15–23	12–20	
Asthma control tes ($n = 11$)	Mean ±SD	20.75 ± 1.67	18.33 ± 2.89	0.109
	Range	18–23	15–20	
Total asthma control test interpretation (n=50)	Well controlled *n* (%)	21 (63.6%)	4 (23.5%)	0.007**
	Not well controlled *n* (%)	10 (30.3%)	5 (29.4%)	0.950
	Very poorly controlled, *n* (%)	2 (6.1%)	8 (47.1%)	0.001**

***p* value< 0.01: highly significant

patients of group 2 (47.1%) compared to those of group 1 (6.1%) (p value=0.001), indicating that asthmatics with IDA suffered from a more severe disease.

Lung function relations with CBC parameters, hemoglobin level, and iron profile

There was a statistically significant association between PFTs' results and hemoglobin level, in which a lower hemoglobin level was associated with worse PFT results, denoting a higher asthma severity (p value=0.03), as presented in Table 4.

In addition, there were statistically significant negative correlations between severity of asthma measured by reduced FEV1/FVC ratio with hemoglobin and ferritin levels in which lower hemoglobin and ferritin levels were associated with lower FEV1/FVC, and higher asthma severity, and vice versa as shown in Table 5 (p value=0.012 and 0.042).

Finally, as shown in Table 6 and Fig. 1, there was a statistically significant positive correlation between MMEF 25 and 75% of predicted with hemoglobin level in which a lower hemoglobin level was associated with a lower MMEF 25–75% results and vice versa denoting a more severe small air way disease in anaemic asthmatics than those with asthma alone (p value=0.012).

Discussion

Asthma is a substantial public health problem worldwide. It is one of the most common chronic diseases in pediatric population [18]. Iron-deficiency anemia (IDA) is frequently seen in pediatric practice [19]. It has already been reported that low hemoglobin level impairs tissue oxygenation [20] and may adversely affect respiratory functions in normal subjects [21, 22].

The current study revealed strong associations between lower iron status and reduced lung function among asthmatic children and therefore higher asthma severity.

To the best of our knowledge, the present study is one of the fewest studies that investigated the influence of low iron status on the lung function in childhood asthma in order to define one of asthma modifiable risk factors hoping to reduce asthma morbidity and severity.

Our analysis found that asthmatics with IDA were more likely to have lower lung function parameters compared to those without IDA (p value =0.012, 0.006, and 0.012) (Tables 1 and 4), which coincided with Eissa et al. [8] who reported in a study conducted on 100 children with upper or lower respiratory tract infection which revealed that pulmonary function parameters were significantly higher among non-anemic asthmatics than among anemic asthmatics.

Table 4 Relations between pulmonary function test results and CBC parameters in the studied patients

Complete blood count parameters	Normal pulmonary function test (*n*=34)	Restrictive airway disease (*n*=1)	Mild obstructive airway disease (*n*=7)	Moderate obstructive airway disease (*n*=3)	Severe obstructive airway disease (*n*=5)	*p* value
Hemoglobin (gm/dl)						
Normal	28 (56.0%)	0 (0.0%)	2 (4.0%)	1 (2.0%)	2 (2.0%)	0.03*
Low	6 (12.0%)	1 (2.0%)	5 (10.0%)	2 (4.0%)	3 (6.0%)	
Haematocrit %						
Normal	26 (52.0%)	1 (2.0%)	4 (8.0%)	1 (2.0%)	2 (4.0%)	0.24
Low	8 (16.0%)	0 (0.0%)	3 (6.0%)	2 (4.0%)	3 (6.0%)	
Mean corpuscular volume (Fl)						
Normal	13 (26.0%)	0 (0.0%)	1 (2.0%)	2 (4.0%)	1 (2.0%)	0.42
Low	21 (42.0%)	1 (2.0%)	6 (12.0%)	1 (2.0%)	4 (8.0%)	
Mean corpuscular hemoglobin (pg.)						
Normal	20 (40.0%)	0 (0.0%)	3 (6.0%)	2 (4.0%)	1 (2.0%)	0.37
Low	14 (28.0%)	1 (2.0%)	4 (8.0%)	1 (2.0%)	4 (8.0%)	
Mean corpuscular hemoglobin cconcentration (g/dl)						
Normal	29 (58.0%)	1 (2.0%)	5 (10.0%)	2 (4.0%)	5 (10.0%)	0.84
Low normal	3 (6.0%)	0 (0.0%)	1 (2.0%)	1 (2.0%)	0 (0.0%)	
Low	2 (4.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	
Platelet's count (10×3)						
Normal	31 (62.0%)	1 (2.0%)	4 (8.0%)	1 (2.0%)	3 (6.0%)	0.05
Low	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	1 (2.0%)	
High	3 (6.0%)	0 (0.0%)	2 (4.0%)	2 (4.0%)	1 (2.0%)	

**p value <0.05 significant*

Table 5 Correlations between severity of asthma with haemoglobin level, iron profile, using Pearson correlation coefficient in asthmatic patients (with and without IDA)

	Severity of asthma	
	r	*p* value
Hemoglobin (gm/dl)	−0.353	0.012*
Red blood cell counts	−0.078	0.591
Transferrin saturation	−0.076	0.601
Total iron (ug/dl)	−0.043	0.765
Ferritin (ng/ml)	−0.248	0.042*

*r Pearson correlation coefficient; *p value <0.05 significant*

A similar observation was reported by Alkhateeb et al. [17] in a study conducted on 100 patients with IDA and 100 children without IDA which stated that those with asthma with anemia had more pronounced deterioration of pulmonary function on spirometry study than those with asthma alone (p value<0.05).

Moreover, several previous studies reported that higher iron stores were inversely associated with asthma and lower body iron and higher tissue iron need were associated with lower lung function [23, 24].

Our findings can be explained by the negative effect of anemia on the strength of respiratory muscles which

Table 6 Correlations between pulmonary function test parameters with haemoglobin level, iron profile, using Pearson correlation coefficient in asthmatic patients (with and without IDA)

	FEV1% of predicted		FVC % of predicted		FEV1/FVC		MMEF 25-75% of predicted	
	r	*p* value	*r*	*p* value	*r*	*p* value	*r*	*p* value
Hemoglobin level (gm/dl)	0.245	0.097	0.126	0.401	0.146	0.327	0.363	0.012*
Red blood cell counts	0.127	0.394	0.226	0.127	−0.203	0.172	0.070	0.642
Transferrin saturation	0.044	0.767	0.043	0.776	0.009	0.950	−0.023	0.877
Total iron (ug/dl)	−0.046	0.757	0.038	0.798	0.108	0.469	−0.012	0.934
Ferritin (ng/ml)	0.105	0.483	−0.013	0.933	0.128	0.389	0.120	0.423

*r: Pearson correlation coefficient; *p value <0.05 significant*

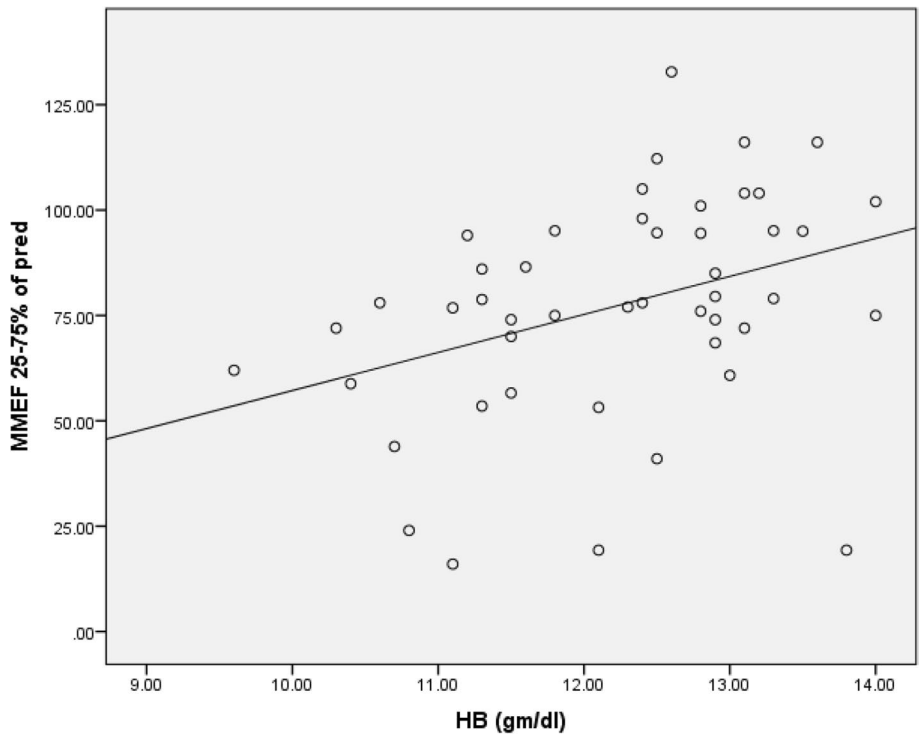

Fig. 1 A positive correlation between MMEF 25–75% and hemoglobin level

reduces the lung function [25, 26]. In addition, iron deficiency impairs the immune system function [26] which increases the risk of respiratory tract infections, thus aggravating the frequency and severity of asthma attacks in asthmatic children which reduces lung function.

The present study showed that a moderate to severe obstructive pattern was significantly observed among asthmatics with IDA than those without ($p = 0.032$) (Table 2). In addition, anemic asthmatic children were more likely to have very poor asthma control than those with asthma alone (p=0.001) (Table 3).

In addition, C-ACT score had a statistically significant negative correlation ($r = -0.399$, $p = 0.012$) with TIBC and a positive one with transferrin saturation (r=0.418, $p = 0.008$) indicating poor asthma control among asthmatics with IDA (data not shown in the results).

These findings are in line with several previously published studies [24, 27, 28], which reported that greater iron stores were inversely associated with asthma and lesser body iron levels were associated with frequent asthma symptoms, poor asthma control, and lower lung function.

Moreover, our study revealed that asthmatic patients with lower lung function tend to have lower haemoglobin and ferritin levels (p value= 0.012 and 0.042) (Table 5). Besides, there was a strong correlation between MMEF 25 and 75% of predicted, and hemoglobin level (p value=0.012) (Table 6, Fig. 1), denoting a more severe small air way disease among anaemic asthmatics than those asthmatics without anemia.

Our findings go parallel with recent studies conducted by Eissa et al. [8] and Alkhateeb et al. [17] who reported a significant direct relation between serum ferritin value and lung function parameters.

Our results are also in conform with Fida and colleagues [28] who found positive correlation between higher hemoglobin and better lung function results in asthmatic children, and also, they added that higher tissue iron needs were correlated with lower lung function.

Furthermore, it was noted by Nwaru et al. [29] and Lanzkowsky et al. [30] that maternal serum ferritin in the 1st trimester was positively correlated with pulmonary function and development of wheezing at 10 years of age.

In contrast to these findings, Brigham et al. [21] reported in a study conducted on 1046 adolescent females in the age group from 12 to 19 years, that no significant relationships were observed between any of the iron indices and lung function, which may be due to low prevalence of IDA among the studied population.

These aforementioned findings of our study declared the substantial effect of iron deficiency on lung function

reduction and poor asthma control and therefore aggravating asthma severity.

Study limitations

The current study has some limitations. First, the sample size was relatively small. Second, the design was cross-sectional and further longitudinal studies are needed to confirm our findings. Finally, this work was a single-center experience; therefore, larger multicentric studies are needed to generalize our results.

Conclusion

IDA is not uncommon in asthmatic children and lower iron status was associated with lower lung function. Therefore, regular screening and early treatment of IDA in asthmatics may be simple, cheap, and cost-effective tool for improving asthma control, enhancing lung function, and reducing asthma severity in low-income societies.

Abbreviations

FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; CBC: Complete blood count; TIBC: Total iron binding capacity; GINA: Global Initiative for Asthma; ACT: Asthma control test; IDA: Iron deficiency anemia; PFTs: Pulmonary function tests; MMEF 25–75%: Maximal mid-expiratory flow; ATS: American Thoracic Society Guidelines; ERS: European Respiratory Society.

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Authors' contributions

HA performed the study design, analyzed and interpreted the patient data, and drafted and wrote the manuscript. TD performed the study design and wrote and revised the manuscript. NR did the patient enrollment and collection of the data. YM shared in paper drafting, and AH analyzed the patient data and drafted the manuscript. The authors revised and approved the manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The Research Ethics Committee of the Faculty of Medicine, Ain Shams University, approved the protocol. Written consent was obtained from the patients' guardians. The reference number is not available at the time being.

Consent for publication

Nothing to declare

Competing interests

The authors declare that they have no competing interests.

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