

Physical growth in children with transfusion-dependent thalassemia

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Objective: To describe physical growth and related factors in transfusion-dependent thalassemia patients.

Methods: This is a cross-sectional analysis of the records of the patients registered at and being followed up by the Thalassemia Day Care Center (TDCC) at Kalawati Saran Children's Hospital, New Delhi, India. Clinical and laboratory parameters were recorded on a spreadsheet for analysis. Clinical parameters included weight, height, sexual maturity ratings, and general and systemic physical examination. Laboratory parameters included pretransfusion hemoglobin (Hb), periodic serum ferritin, and tests for viral markers of human immunodeficiency virus (HIV) and hepatitis B and C. Z-scores for weight, height, and body mass index (BMI) were calculated using World Health Organization reference data. Statistical analysis was carried out using Microsoft Excel® and Stata® software.

Results: Out of 214 patients registered at the TDCC since 2001, 154 were included in this study. The mean age of patients was 9.19 years (range 0.5–20 years). Pretransfusion Hb was well maintained (mean 9.21 g/dL; 95% confidence interval [CI]: 9.06–9.36), but the mean serum ferritin levels were approximately three times (3112 ng/mL) the desired value despite the patients being on deferiprone (72%) or deferasirox (25%). One-third (33.11%) of the patients had short stature, 13% were thin, and 10.82% were very thin (BMI z-score <−3). No patient was overweight or obese. Linear regression coefficient showed that for every 1-year increase in age, the mean ferritin value increased by 186.21 pg/mL (95% CI: 143.31–228.27). Height z-scores had significant correlation with mean ferritin levels, whereas correlation with mean pretransfusion Hb was not significant statistically. Mean ferritin levels were significantly higher in patients with short stature than in the patients with normal height. Regression analysis showed that an increase of 3571 units of serum ferritin was associated with a decrease of one point in height z-scores. One-fifth (19.40%) of adolescent patients had delayed puberty.

Conclusion: Approximately one-third (33.11%) of patients with transfusion-dependent thalassemia major were of short stature. In this group of patients with pretransfusion Hb levels maintained at desired levels, physical growth was correlated with status of iron overload.

Keywords: thalassemia, growth, body mass index, serum ferritin

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Introduction

Thalassemia major is a heterogeneous disease presenting during infancy or early childhood. Although thalassemia is preventable by premarital counseling and prenatal testing, a large number of children are born with thalassemia, and curative treatment in the form of bone marrow or stem cell transplantation is not possible for the majority of these patients. Such patients need regular transfusions of packed red blood cells

(PRBCs) and iron chelation along with close monitoring and treatment for complications of the disease.

Physical growth is affected in a large number of the patients with transfusion-dependent thalassemia. A study of patients aged 10–27 years with thalassemia major found short stature in 70% of the males and in 73% of the females.¹ Another study found short stature in 29.7% of patients.² The etiological factors leading to growth retardation in transfusion-dependent thalassemia are varied, with iron overload-induced endocrinopathies, chronic anemia, and folate and zinc deficiencies having been implicated in this complication.^{3,4} A close monitoring of growth may lead to early identification and treatment of these complications to ensure that patients achieve near normal adult height.

India has a large number of young patients with transfusion-dependent thalassemia, and very few studies have reported the issues related to physical growth in these children.^{5,6} We present here our experience of managing children with transfusion-dependent thalassemia, with a focus on their physical growth.

Material and methods

This was a cross-sectional study of patients with transfusion-dependent thalassemia registered at the Thalassemia Day Care Center (TDCC) at Kalawati Saran Children's Hospital, New Delhi, India. All the patients registered at the TDCC had a confirmed diagnosis of thalassemia major on the basis of hemoglobin (Hb) electrophoresis and the patients' need for regular blood transfusion.

At the time of registration, all patients had a detailed clinical examination and laboratory tests, including a hemogram, liver function test, and screening for hepatitis B, hepatitis C, and human immunodeficiency virus (HIV). Most of the patients visited the TDCC every 3–4 weeks for blood (packed cell) transfusion. At this time, in addition to clinical data, a hemogram was done for all patients. Serum ferritin and calcium levels were recorded at the time of registration and every 3 months. Screening for hepatitis B, hepatitis C, and HIV was repeated every 6 months. The first ferritin level was measured after 15 blood transfusions, and if the level was found to be >1000 ng/mL, then iron chelation was started with deferiprone at a dosage of 75 mg/kg/day. Deferasirox (35–40 mg/kg/day) was started when the patient's family could afford it and when adverse effects were observed with deferiprone. Serum ferritin levels were tested every 3 months. Thyroid function tests and echocardiography were done every year in children over 10 years of age. Other tests

were done whenever clinically indicated. All this information was recorded in patient case records.

The records of all the registered patients were reviewed in July 2009. Information on the number of transfusions received, pretransfusion Hb levels, and serum ferritin levels done in the previous 6–12 months was obtained from these records. Complete clinical examination was also performed during this period. Height was recorded using a stadiometer to the nearest 0.1 cm, and weight was measured in minimal clothes to the nearest 0.1 kg. An assessment of sexual maturity rating (SMR) was done in all the patients 10 years or older. SMR staging was done for breast stage in girls and testicular volume in boys and for pubic hair in both.⁷ Delayed puberty was defined by non-appearance of breast buds or pubic hairs by 14 years of age in girls and no increase in testicle volume greater than 4 mL and no pubic hairs by 15 years of age in boys.

To calculate the *z*-score of an observed value, the following formula was used:

$$z\text{-score} = [(observed\ value \div M)^L - 1] / L \times S.$$

In this formula, M, L, and S are values for the reference population. M is the reference median value, which estimates the population mean. L is the power needed to transform the data in order to remove skewness (ie, to normalize the data). S is the coefficient of variation (or equivalent).⁸ This formula, sometimes called the LMS formula, was used to calculate *z*-scores for weight-for-age, height-for-age, and body mass index (BMI)-for-age. LMS values for age and sex were copied from the World Health Organization (WHO) 2007 growth reference expanded tables for constructing national health charts⁹ and were transferred to a data spreadsheet where the *z*-score formula was written and *z*-scores were calculated for above parameters of every patient. The *z*-scores were used for various comparisons and statistical tests. Because nationally representative data on growth during adolescence are not available exclusively from India, and the WHO 2007 growth study included children from India, these data were used in this study for calculating *z*-scores.

Mean, standard deviation, 95% confidence interval (CI), and minimum and maximum values were calculated for various parameters. Proportions or percentages were also calculated wherever needed. Means were compared by Student's *t*-test. Correlation and regression analyses were also done to test relationships between the parameters. Microsoft Excel® (Redmond, WA, USA) and Stata software (StataCorp, College Station, TX, USA) were used for data analysis and statistical tests.

Data on physical growth and its correlates are presented in this article. Details of iron chelation and endocrinologic issues are being published separately.

Results

The TDCC began operating in 2001 and, to date, 214 patients are registered. The current analysis includes 157 (73.36%) of these patients. Out of the remaining 57, 17 died, 18 were transferred to the Department of Medicine when they reached 20 years of age, one patient underwent bone marrow transplant and was being followed up at another institute, and 21 patients were lost to follow-up, as shown in Figure 1. The clinical and laboratory characteristics of these patients are described in Tables 1 and 2, respectively.

Age ranges of the subjects were from 6 months to 20 years. Mean age was 9.19 years. There was an almost equal distribution of patients from infancy to adolescence. There was a slight preponderance of males (57.96%) compared with females (42.04%).

Pretransfusion Hb levels were well maintained, with mean levels being 9.21 g/dL, (95% CI: 9.06–9.36, range 5.8–11.8 g/dL). Almost half (44.30%) of the patients had

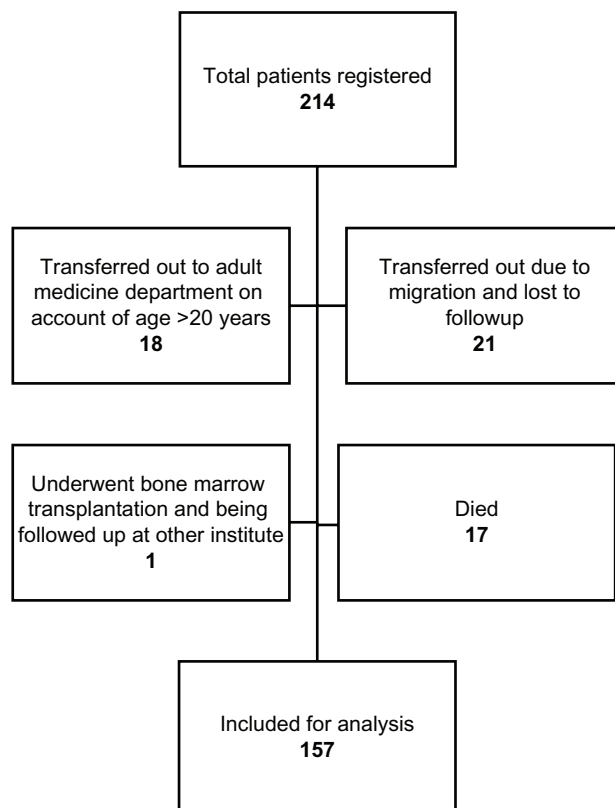


Figure 1 Flow chart showing number of patients registered, died, lost to follow-up, transferred out, and continuing in follow-up (included for analysis).

Table 1 Clinical parameters of children with transfusion-dependent thalassemia

Parameters	Number (%)	Range
Total number	157 (100%)	
Males	91 (57.96%)	
Mean age \pm SD (years)	9.19 \pm 4.60	0.5–20
Mean weight z-score ^a	-1.33 \pm 0.85	-4.09–0.59
Number (%) of patients with weight z-scores < -2	21 (13.37%)	
Mean height z-score	-1.60 \pm 1.24	-5.99–1.86
Number (%) of patients with height z-scores < -2	52 (33.11%)	
Mean BMI z-score	-1.44 \pm 1.36	-7.07–0.97
Number (%) of patients with BMI z-scores < -2	38 (24.19%)	
Hepatomegaly (liver > 1 cm below costal margin)	48 (30.57%)	
Splenomegaly (spleen > 1 cm below costal margin)	73 (46.49%)	
Delayed puberty ^b (male)	4/23 (17.39%)	
Delayed puberty ^b (female)	9/44 (20.45%)	
Splenectomized	9 (9.73%)	
Prescribed deferiprone	113 (71.97%)	
Prescribed deferasirox	40 (25.47%)	

Notes: ^aWeight z-scores could be calculated up to 10 years of age only, as World Health Organization data for weight z-scores are not available beyond 10 years of age; ^bAssessed only in patients in adolescent age group (10–20 years).

Abbreviations: SD, standard deviation; BMI, body mass index.

pretransfusion Hb levels above 9.5 g/dL, and only one patient presented with Hb 5.8 g/dL. Mean pretransfusion Hb was significantly higher in females (9.46 g/dL) than in their male (9.03 g/dL) counterparts ($t = 2.76$, $P < 0.0032$).

Mean ferritin level was 3112 ng/mL. The minimum value (785 ng/mL) was observed in a new patient, and the maximum value (7474 ng/mL) was observed in a 14-year-old boy. The difference between the mean ferritin levels of male and female patients was not statistically significant. The majority of our patients (153 of 157, or 97.45%) were on iron chelation

Table 2 Laboratory parameters of children with transfusion-dependent thalassemia

Mean ferritin (ng/mL)	3138 \pm 1499	785–7474
Number (%) with mean ferritin (ng/mL) levels:		
<2000	49 (31.21%)	
2000–5000	92 (58.60%)	
>5000	16 (10.19%)	
Mean pretransfusion Hb (gram/dL)	9.21 \pm 0.97	5.8–11.8
Hepatitis B positive	11 (7.00%)	
Hepatitis C positive	5 (3.18%)	
HIV positive	10 (6.36%)	

Abbreviations: Hb, hemoglobin; HIV, human immunodeficiency virus.

therapy (ie, deferiprone [71.97%] or deferasirox [25.47%]). The remaining four patients were considered to be too young for iron chelation therapy and had serum ferritin levels less than 1000 ng/mL.

The mean z-score for weight-for-age was within the normal range (-1.33 ± 0.85), and only 21 (13.37%) of the patients were underweight (weight-for-age z-scores below -2). One-third of the patients (33.11%) had short stature (height-for-age z-scores < -2), and one-quarter of patients (24.11%) were undernourished (thinness in 13% of the patients and severe thinness in 10.82%; BMI-for-age z-scores < -2 and < -3 , respectively). None of the patients was overweight or obese. Although minor variations were found in these parameters in males and females, the differences were not statistically significant.

Correlations between age (years) and weight z-scores, height z-scores, BMI z-scores, mean ferritin levels, and mean pretransfusion Hb were calculated. There was a significant and positive correlation between age and mean ferritin level (correlation coefficient [r] = 0.6085, $P = 0.000$). Linear regression coefficient between age and mean height z-scores was -0.1160388 (95% CI: -0.0772262 – 1.583013 , $P = 0.000$). This suggests that for every 1-year increase in age, the mean height z-scores declined by -0.11

(95% CI: -0.0772262 – 1.583013). Linear regression coefficient between age and mean ferritin levels was 186.21 (95% CI: 143.31–228.27, $P = 0.000$). This suggests that for every 1-year increase in age, the mean ferritin value increased by 186.21 ng/mL (95% CI: 143.31–228.27).

Correlation coefficients of height-for-age and BMI-for-age z-scores with mean ferritin levels and pretransfusion Hb levels were calculated. height-for-age z-scores and mean ferritin levels were negatively correlated, as indicated by a correlation coefficient between the two of -0.3415 ($P = 0.000$), as shown in Figure 2. However, the mean pretransfusion Hb levels were not related ($r = 0.0218$, $P = 0.788$). Although BMI-for-age showed significant correlation with mean ferritin levels ($r = -0.2478$, $P = 0.002$) and with mean pretransfusion Hb ($r = 0.1816$, $P = 0.024$), the strength of association was poorer than that for mean ferritin levels.

Regression analysis between height z-scores and mean ferritin levels was significant (regression coefficient -0.0002872 , standard error 0.0000626, $t = -4.59$, $P = 0.000$), meaning that for every 1000 unit increase in mean ferritin levels, the height z-scores changed by -0.28 (95% CI: -0.41 to -0.16 , $P = 0.000$) units. In other words, an increase of 3571 units of serum ferritin was associated with a decrease of one point in the height z-scores.

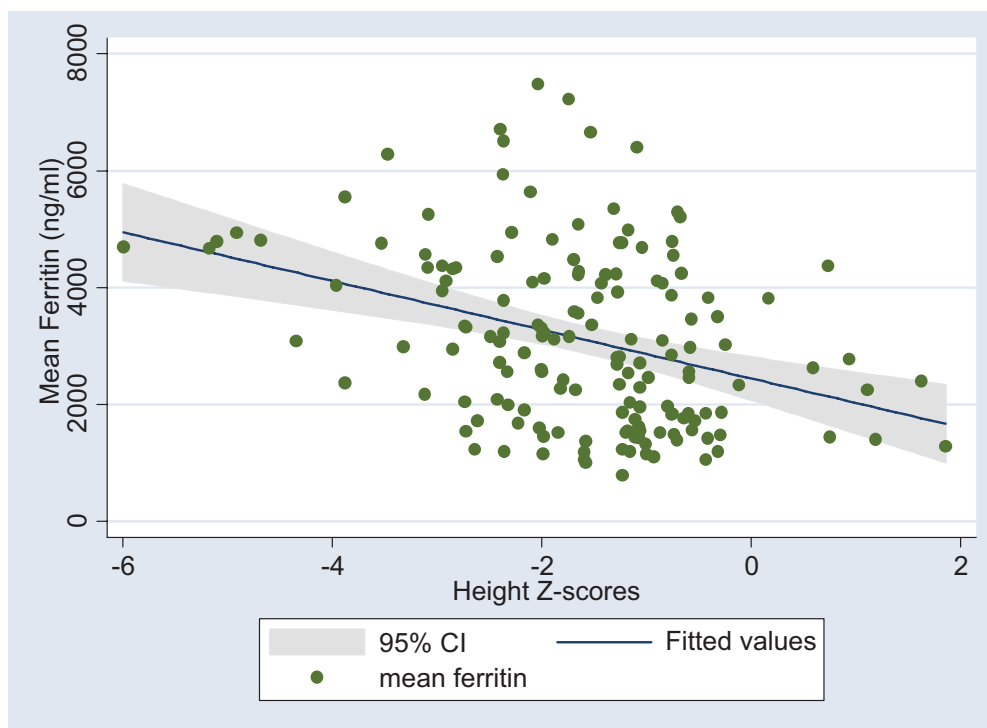


Figure 2 Regression fit between mean serum ferritin levels (ng/mL) and height z-scores in children with transfusion-dependent thalassemia. **Abbreviation:** CI, confidence interval.

Table 3 Height z-score according to age and serum ferritin levels in children with transfusion-dependent thalassemia

Serum ferritin (ng/mL)	<5 years		5–10 years		>10–15 years		>15 years		All	
	Number	Height z-score	Number	Height z-score	Number	Height z-score	Number	Height z-score	Number	Height z-score
<2000	21	-0.96 ± 1.08	22	-1.13 ± 0.62	4	-0.86 ± 1.21	2	-2.17 ± 0.26	49	-1.080.90
>2000	6	-0.79 ± 0.46	45	-1.10 ± 1.00	43	-2.65 ± 1.1	14	-2.09 ± 1.44	108	-1.831.31
<i>P</i> value ^a		0.71		0.89		0.00		0.94		0.00

Note: ^a*P* values for Student's *t*-test between height z-scores in patients with serum ferritin levels <2000 or >2000.

The regression between height z-score and mean pretransfusion Hb levels was not statistically significant. Regression analysis between BMI z-scores and serum ferritin levels revealed that for every 1000 unit reduction in serum ferritin levels, BMI z-scores increased by 0.21 (95% CI: -0.34 to -0.07, *P* = 0.003).

The results of nonparametric regression analysis (bootstrap regression and multivariate regression) of height z-score and BMI z-score with mean ferritin levels and mean pretransfusion Hb levels were similar to the results given previously.

The relationship of height z-scores with mean serum ferritin levels and mean pretransfusion Hb was further substantiated by comparing these parameters in patients with height z-scores <2 with those with scores ≥2. Mean ferritin levels were significantly higher in short-statured (height z-score <2) patients in comparison with patients with normal height (3720 ± 1512 mg/L vs 2570 ± 1196 mg/L, *P* = 0.000). Differences in pretransfusion Hb levels were not statistically significant in these groups. Height z-scores were further studied at different ages according to ferritin levels (Table 3). It is evident that height z-scores were significantly different in patients with serum ferritin levels less than or greater than 2000 ng/mL when all patients were considered together. Age-stratified analysis revealed that this difference was significant only in 10–15-year-old children.

One-fifth (19.4%) of adolescent patients in this study had delayed puberty. When compared with patients with pubertal development, the height z-scores, BMI z-scores, serum ferritin levels, and pretransfusion Hb levels were not different statistically.

The prevalence of hepatitis B, C, and HIV was low in our patients, as they receive properly tested blood. Only a minority (9.73%) of patients required splenectomy.

Discussion

When bone marrow transplant is not feasible for medical or financial reasons, regular PRBC transfusion is the mainstay of treatment for thalassemia major patients. However, this brings some undesired effects by leaving a deposit of iron

in various organ systems. It therefore becomes important to reduce this harm by chelating excess iron and monitoring the side effects. Our patients received regular transfusions of PRBCs, and all of those who were eligible to receive iron chelation agents were prescribed either deferiprone (75%) or deferasirox (25%). They were monitored clinically and required regular laboratory tests.

Despite regularly using iron-chelating agents, the mean ferritin level in our patients was 3138 ng/mL, which is almost three times the desired level of 1000 ng/mL. However, 31% of our patients had serum ferritin levels <2000 ng/mL, and only 10% of patients had levels >5000 ng/mL. The mean pretransfusion Hb amount (9.21 g/dL) was near to the desired level of 9.5 g/dL. Thus, our patients received PRBCs in nearly adequate amounts, but the iron chelation could not be achieved as desired.

The mean levels of serum ferritin depend on several factors, including age at presentation, age at beginning regular PRBC transfusion, age at starting iron chelation therapy, efficacy of the iron chelation drug and its compliance, and the age group of the reported series of patients. Our observed high ferritin levels among our thalassemic patients are consistent with serum ferritin levels of 2729 ng/mL (6579 pmol/L) observed in 11–19-year-old transfusion-dependent thalassemia major patients in Hong Kong.² However, low levels (2013 ng/mL/4525 pmol/L) were found in patients younger than 11 years of age in this series. Observation of nontransplanted thalassemia major patients in the national registry of France indicates that better-managed patients may have lower serum ferritin levels (1240 ng/mL).¹⁰

This excess iron store, as shown by increased ferritin values, seems to mediate several of the complications of thalassemia. In well-transfused patients, poor compliance to chelation treatment and subsequent iron overload remain the main causes of poor growth.¹¹

About one-third (33.11%) of our patients had short stature, and 24.19% of our patients were thin or severely thin. Height-for-age was related to mean ferritin levels

($r = -0.3415$, $P = 0.000$) and not to mean pretransfusion Hb levels ($r = 0.0218$, $P = 0.788$). This suggests that it is not chronic hypoxia (by anemia) but excess iron that is responsible for short stature. This fact is better shown by the regression fit analysis highlighted in Figure 2. It indicates that every increase of ferritin by 3571 ng/mL led to a reduction of height by one unit z -score. Although such approximations can be better predicted by a longitudinal study, several studies have noted similar findings. A study from Israel found that high serum ferritin levels (>3000 ng/mL) during prepubertal age were related to final short stature.¹² Another study from Malaysia revealed that the mean serum ferritin level of thalassemics with a height under the third percentile was higher compared with those with a height over the third percentile (4567.0 ng/mL vs 2271.0 ng/mL, $P = 0.01$).¹³

We also had similar findings, as serum ferritin levels were significantly higher in our patients with short stature (height z -score <-2) in comparison with those normal stature. Further, the height z -scores of our patients with serum ferritin >2000 ng/mL were significantly lower than of those with serum ferritin levels <2000 ng/mL. These observations substantiate the fact that it is the deposition of iron (represented by serum ferritin levels) that mediates growth retardation, even when chronic hypoxia (represented by mean pretransfusion Hb < 9.5 g/dL) is not observed. An earlier study from India found no relation between physical growth and serum ferritin levels.⁶ This is contrary to our study where we found that the higher the serum ferritin level, the lower the height z -score.

We observed that short stature becomes more prominent during early adolescence (10–15 years of age). Even serum ferritin levels did not make any difference prior to or beyond this age (Table 2). Delayed puberty in these patients probably mediated this short stature. A longitudinal study of transfusion-dependent thalassemia patients may further clarify this relation. Somewhat similar observations were found in a study from Iran, which indicated that 70% of boys and 73% of girls over 10 years of age with transfusion-dependent thalassemia had short stature.¹ The final adult height depends on the efficacy of iron chelation, especially during prepubertal years.¹² Therefore, to attain a near normal adult height, iron chelation should be started at an appropriate time, particularly when serum ferritin levels reach 1000 ng/mL and a good compliance should be ensured. More efficient iron-chelating drugs are needed to reduce or possibly prevent the complications related to deposition of iron. Some drugs, including deferitron, are under development.¹⁴

About one-fifth of our adolescent patients had delayed puberty. A varied proportion of patients with delayed puberty or hypogonadism have been reported. A study from Tehran reported delayed puberty in 12.4% of girls and 22.5% of boys with thalassemia major.¹⁵ Other studies found higher percentages of patients, eg, up to 73% of girls and 70% of boys¹ and 38.4% of adolescents² with delayed puberty or hypogonadism. Soliman et al found no pubertal changes in 73% of boys and 42.7% of girls.¹⁶ Gonadal failure is related to age at starting iron chelation therapy. Patients with high serum ferritin levels more commonly experience gonadal failure.¹⁷ However, ferritin levels in our patients with delayed puberty were not significantly different from those in adolescent patients with normal puberty. Only a small number of our patients had delayed puberty, which was diagnosed clinically by SMR ratings only. Detailed endocrinological/hormonal evaluation could probably provide a better insight into this observation.

To summarize, regular blood transfusions can maintain pretransfusion Hb levels, but if serum ferritin levels are higher than the desired levels, patients' physical growth can be affected. Thus, along with maintaining Hb levels, it is important to have effective iron chelation therapy to minimize retardation of growth in patients with transfusion-dependent thalassemia. Thalassemia patients requiring regular blood transfusions need better strategies for removing excess iron from their bodies.

Disclosure

The authors report no conflicts of interest in this work.

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