—Original—

Iron Supplementation for Hypoferritinemia-Related Psychological Symptoms in Children and Adolescents

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Background: Although some studies have described the association between serum ferritin levels and specific disorders in child and adolescent psychiatry, few have focused on mental status *per se* with low serum ferritin levels in children and adolescents. This study examined the effects of iron administration on psychological status of children and adolescents with reduced serum ferritin concentration.

Methods: This prospective study evaluated 19 participants aged 6-15 years with serum ferritin levels <30 ng/mL who visited a mental health clinic and received oral iron administration for 12 weeks. The participants were assessed using the Clinical Global Impression Severity (CGI-S), Profile of Mood States 2nd Edition Youth-Short (POMS), Center for Epidemiologic Studies Depression Scale (CES-D), and Pittsburgh Sleep Quality Index (PSQI). In addition to serum ferritin, blood biochemical values such as hemoglobin (Hb) and mean corpuscular volume (MCV) were examined. School attendance was recorded.

Results: The most prevalent physical symptoms were fatigability and insomnia. The CGI-S, PSQI, and CES-D scores decreased significantly following iron supplementation, whereas the scores of almost all POMS subscales improved significantly at week 12. No participant had hemoglobin levels <12 g/dL. Serum ferritin concentration increased significantly, whereas Hb and MCV remained unchanged. At baseline, 74% of the participants did not attend school regularly; this number improved to varying degrees by week 12.

Conclusions: Serum ferritin levels would be preferable to be measured in children and adolescents with insomnia and/or fatigability regardless of psychiatric diagnoses or gender. Iron supplementation can improve the hypoferritinemia-related psychological symptoms of children and adolescents, such as poor concentration, anxiety, depression, low energy and/or irritability. (J Nippon Med Sch 2022; 89: 203–211)

Key words: ferritin, iron supplementation, children, adolescents, psychiatry, mental health

Introduction

Iron stores exist in the body primarily in the form of ferritin[1]. The ferritin molecule is an intracellular hollow protein shell, and small amounts of ferritin are secreted into the plasma[1]. This plasma ferritin is in equilibrium with tissue stores, and its concentration declines early during the development of iron deficiency[2]. Thus, the concentration of serum ferritin is positively correlated with the size of the total body iron stores in the absence of inflammation[1], suggesting that low serum ferritin concentration is a non-invasive, sensitive indicator of iron deficiency[2]. The generally accepted serum ferritin cut-off value at which iron stores are considered to be depleted is 15 ng/mL for individuals aged 5 years and older[1,2]. Meanwhile,

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there is a recent report that ferritin levels lower than 30 ng/mL indicate iron deficiency, even if hemoglobin (Hb) content is within the normal range[3].

Numerous studies have established a relationship between poor cognitive and motor development and iron deficiency anemia in infants and young children. Children with iron deficiency have a concurrent and future risk of poor development[4]. However, there is a lack of concrete evidence to conclusively state that short-term iron therapy improves psychomotor development and cognitive function in children with iron deficiency anemia aged below three years[5]. In addition, there is limited evidence to recommend iron therapy to improve the developmental outcome of pre-school children with non-anemic iron deficiency[6]. Furthermore, the relation between iron deficiency and mental status in school-age children and adolescents has not been investigated in detail.

Some psychiatric studies on children and adolescents have reported on the relationship of serum ferritin concentration with specific disorders. Reduced serum ferritin is recognized for its association with sleep disorder due to restless leg syndrome (RLS)[7], as well as with attention-deficit/hyperactivity disorder (ADHD)[8,9] and tic severity[10]. In RLS, iron administration is recommended when serum ferritin is lower than 50 ng/mL[7]. However, only few studies have focused on serum ferritin concentration to specifically investigate the effect of iron supplementation on psychological symptoms *per se*, and not particular psychiatric disorders, in children and adolescents. We first evaluated the effect of oral iron administration on the psychological and physical symptoms of children and adolescents with reduced serum ferritin concentrations[11], retrospectively showing that iron administration improves anxiety, poor concentration, depression, fatigability, and/or insomnia.

Given those, we hypothesized that low serum ferritin level would affect the mental status in children and adolescents. The aim of this study was to prospectively elucidate the effect of iron administration for 12 weeks on the psychological status of children and adolescents with reduced serum ferritin concentration.

Methods

Participants

This was an open-label study, and included patients from the outpatient clinic of the Department of Psychiatry at Tokai University School of Medicine. The inclusion criteria were as follows: Age 6-15 years; serum ferritin levels lower than 30 ng/mL; and presence of fatigability, insomnia, irritability, and/or low energy. These physical symptoms were selected based on our previous study[11], and evaluated through self- and other-reports from the child and their parents, respectively. The exclusion criteria were as follows: current administration of psychotropic drugs; severe physical diseases such as malignancy, infection, or endocrine illness; or a diagnosis of schizophrenia or epilepsy. The presence of physical diseases was used as an exclusion criterion because ferritin is also an acute-phase protein; thus, acute and chronic diseases can increase ferritin concentration[2]. The discontinuance criteria following study initiations were as follows: Starting psychotropic drug treatment for a psychiatric disorder, starting vasopressor treatment for orthostatic intolerance (OI), or discontinuing oral iron administration; severe physical disease; or withdrawal of consent. Participants who had been taking vasopressors for OI prior to entering this study were included and continued their treatment at the same, prior dose throughout the study. All participants took 25-100 mg iron orally for 12 weeks. To evaluate the effect of iron supplementation more extensively, we did not conduct a special psycho-social therapy. All the patients were treated with usual psychotherapy, such as supportive psychotherapy, psycho-educational therapy for understanding a psychiatric disorder, and/or advice for improving daily living conditions.

This study was approved by the Institutional Review Board for Clinical Research at Tokai University School of Medicine (ref, #17R280). Written informed consent was obtained from children and their legal guardians. This prospective study was registered with the UMIN Registry (ref, UMIN000031935; date of registration, 28/03/2018).

Measures

The primary endpoint was the difference in CGI Severity (CGI-S) at baseline and week 12. In addition, CGI Improvement (CGI-I) was assessed as an indicator of improvement at week 12. The CGI, which is an assessment of an individual's overall global functioning, has been successfully used in children[12,13]. Participants were further evaluated at baseline and week 12 of iron administration using the Center for Epidemiologic Studies Depression Scale (CES-D)[14,15], the Profile of Mood States 2nd Edition Youth-Short (POMS)[16–18], and the Pittsburgh Sleep Quality Index (PSQI)[19,20] to evaluate the degree of improvement of their psychological status and quality of sleep. The CES-D evaluated depressive state and has been used for the

assessment of children[21]. The cut-off point was a score of 15/16, with higher scores indicating greater symptoms of depression. The POMS targeting youth aged 13-17 years contains a subset of 35 items from the full-length version. It has been found to be particularly useful in measuring changes in affect and mood over time, and evaluating anger-hostility (POMS-AH), confusion-bewilderment (POMS-CB), depression-dejection (POMS-DD), fatigue-inertia (POMS-FI), tension-anxiety (POMS-TA), vigor-activity (POMS-VA), and friendliness (POMS-F). Standardized scores obtained by converting raw scores were used for analysis[18]. Higher scores indicated more severe symptoms for all subscales except POMS-VA and POMS-F. At a score 60 or higher, mood state was considered clinically serious for all subscales except POMS-VA and POMS-F, which were considered serious at a score less than 40. The PSQI was used to assess subjective sleep quality. The cut-off point was 5.5, with higher scores indicating more severe symptoms of insomnia and has been used to assess sleep quality in children[22,23]. Assessments were conducted through discussion between children and their legal guardians since children may have difficulty understanding these scales.

The PSQI, however, is not sensitive to detecting difficulty awakening in the morning, which should be considered in the case of insomnia in children. Therefore, we created a questionnaire to measure awake state in the morning that was based on and adapted from the Children's Sleep Habits Questionnaire (CSHQ)[24,25]. The relevant part of the original questionnaire that focused on difficulty awakening in the morning consisted of the following four factors: 1) the child wakes up in negative mood, 2) adults or siblings wake the child up, 3) the child has difficulty getting out of bed in the morning, and 4) the child takes a long time to become alert in the morning. A numerical rating from 1 to 3 was then assigned based on the frequency of these events, wherein a score of 3 represented 5 or more times a week; 2 was for 2-4 times a week; and 1 was never or once a week. The range of the scores was 4 to 12; the higher the total score, the more difficult children were to awake in the morning. In addition, we assessed school attendance. To objectively assess this, we originally set a following numerical scoring system wherein 3 represented non-attendance; 2 represented attendance less than half of a week; 1 represented attendance half or more of the week, or tardiness almost every day; and 0 represented attendance at school. The range of scores was 0 to 3; the higher the score, the less children attended school. This questionnaire was named the "Mini Scale for Attendance at School (MSAS)."

Psychiatric diagnosis was carried out using the Mini International Neuropsychiatric Interview (MINI)[26,27] for Children (MINI-KID)[28], based on the Diagnostic and Statistical Manual of Mental Disorders (fourth edition). All diagnoses were verified using Diagnostic and Statistical Manual of Mental Disorders (fifth edition) (DSM-5).

Blood biochemical values of Hb, mean corpuscular volume (MCV), iron, total iron binding capacity (TIBC), and ferritin were measured at baseline and week 12.

Statistical Analysis

Continuous variables are presented as mean with standard deviation (SD). Categorical variables were analyzed by applying descriptive statistical methods. Continuous variables were compared using the Mann-Whitney U test. To identify differences in scores between baseline and week 12, Wilcoxon's signed rank tests were used. The effect of psychiatric disorder on outcome (CGI-I) was evaluated using the Mann-Whitney U test. The risk factor for baseline CGI-S was examined using proportional odds model. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used for data analysis.

Results

Physical Exam

Twenty participants were enrolled in the current study. One participant withdrew consent; therefore, the remaining 19 were finally included in analyses and followed up from March 2018 to March 2019.

The mean number (SD) of outpatient visits for 12 weeks was 5.6 (1.8). One child, aged 6 years, attended kindergarten, while the remaining participants attended elementary or junior high school. Results from physical examination of the 19 participants before taking oral iron are presented in **Table 1**. The most prevalent physical symptoms were fatigability and insomnia (either difficulty falling asleep, arousal during sleep, or difficulty awakening in the morning). Other notable symptoms included troublesome feelings, daytime somnolence, nausea, lightheadedness, and dark circles under the eyes. Three participants experienced restress leg; among them, one was diagnosed as having RLS according to the DSM-5.

Psychiatric Diagnoses and Psychological Symptoms

Seven participants were diagnosed as having adjustment disorder; four as having general anxiety disorder and autism spectrum disorder; three as having ADHD; two as having major depressive disorder; and one each

Table 1 Physical examination of participants before iron administration

	n = 19
Age, mean (SD)	11.2 (2.4)
Height (cm), mean (SD)	146.8 (15.5)
Weight (kg), mean (SD)	40.6 (10.7)
Systolic blood pressure, mean (SD)	110.6 (10.7)
Diastolic blood pressure, mean (SD)	65.1 (9.4)
Physical symptoms	
Fatigability, n (%)	19 (100)
Insomnia	19 (100)
Difficulty awakening in the morning, n (%)	19 (100)
Difficulty falling asleep, n (%)	11 (58)
Arousal during sleep, n (%)	9 (47)
Troublesome feeling, n (%)	17 (90)
Daytime somnolence, n (%)	13 (68)
Nausea, n (%)	13 (68)
Lightheadedness, n (%)	12 (63)
Dark circles under eyes, n (%)	11 (58)
Desire to eat something cold, n (%)	10 (53)
Abdominal pain, n (%)	9 (47)
Headache, n (%)	8 (42)
Restless legs, n (%)	3 (21)

having separation anxiety disorder, panic disorder, social anxiety disorder, and no diagnosis. These diagnoses occasionally overlapped. The number (%) of the participants with serious symptoms of POMS (score ≥60) was as follows: POMS-CB, 17 (89); POMS-DD and POMS-TA, 13 (68); POMS-AH and POMS-FI, 12 (63).

The results of CGI, POMS, and PSQI are shown in **Figure 1**. The mean scores of CGI, PSQI, and subscales of POMS (POMS-AH, -CB, -DD, -FI, and -TA) at baseline were clinically serious; however, at week 12, they were in the mild to normal range. In addition, the mean score (SD) of CES-D was significantly lower at week 12 (baseline, 29.5 (10.2); week 12, 20.2 (11.8); P = .0009), and the mean score (SD) of awake state in the morning significantly improved at week 12 (baseline, 10.7 (2.4); week 12, 7.5 (2.1); P = .0014).

Six out of 19 participants had a diagnosis of OI (one had a provisional diagnosis) from pediatric service before visiting our Psychiatry Department. Two of the six participants had been treated with midodrine for OI prior to initiation of iron administration, and the treatments with midodrine continued at the same dose during the study period.

To avoid bias due to the existence of ADHD, a subanalysis without the four participants with ADHD was performed. The mean scores of CGI, PSQI, and subscales of POMS (POMS-AH, -CB, -DD, -FI, -TA, and VA) were significantly lower at week 12 compared with those at baseline.

Risk factors for worse clinical outcome due to CGI-I were examined using the Mann-Whitney U test. The mean CGI-I score (SD) of participants with major depressive disorder was significantly higher than those with other diagnoses (participants without depression, 2.0 (0.8); those with depression, 3.5 (0.7); P = .0351).

Blood Sample Analysis

No participants had shown signs of anemia (Hb <12 g/dL). Blood biochemical data are shown in **Table 2**. All biochemical values at baseline were similar between the 11 male and eight female participants. Within the female participants, the biochemical values were similar between the menstruating (n = 4) and non-menstruating (n = 4). Twelve participants had a family history of anemia; however, biochemical values at baseline were not different between those with and without this history.

All participants took 25-100 mg iron orally during the observation period. Nausea was noted as an adverse effect in six participants, and epigastric discomfort or constipation was noted in one participation each.

The risk factor for baseline CGI-S was examined using proportional odds model. Higher CGI-S was associated with lower serum ferritin levels (odds ratio 1.17 for 1.0

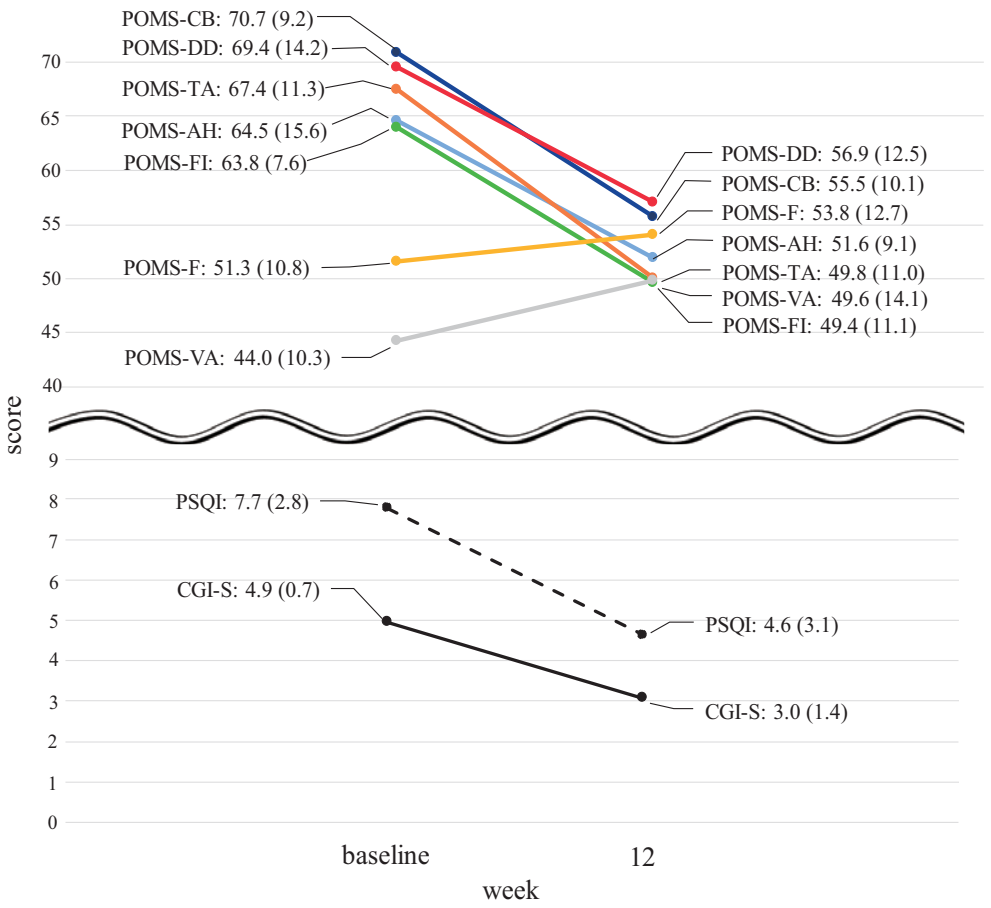

Fig. 1 Effect of iron administration on the psychological state of subjects

The mean number (SD) is shown. The data at week 12 were compared with those at baseline. All of the Profile of Mood States 2nd Edition Youth-Short (POMS) scores, except vigor-activity (POMS-VA) and friendliness (POMS-F), significantly decreased at week 12 (anger-hostility (POMS-AH), $P = .0009$; confusion-bewilderment (POMS-CB), $P < .0001$; depression-dejection (POMS-DD), $P = .0003$; fatigue-inertia (POMS-FI), $P = .0001$; tension-anxiety (POMS-TA), $P < .0001$). The score for POMS-VA significantly increased at week 12 ($P = .0032$), but not the POMS-F score ($P = .3573$). There was a significant decrease at week 12 in the Clinical Global Impression Severity (CGI-S) score ($P < .0001$). A significant decrease in the Pittsburgh Sleep Quality Index (PSQI) score was also noted at week 12 ($P = .0010$).

Table 2 Courses of blood biochemical values

	baseline			p*	3 months	p†
	total (n = 19)	male (n = 11)	female (n = 8)		total (n = 18) ‡	
Hb§, g/dL (SD)	13.9 (0.9)	14.2 (0.9)	13.5 (0.8)	.0784	14.1 (0.9)	.1431
MCV§, fL (SD)	85.0 (3.3)	84.2 (2.8)	86.1 (3.8)	.1336	85.4 (3.7)	.2396
Iron, μg/dL (SD)	90.1 (23.9)	82.4 (26.0)	100.6 (16.7)	.0531	112.2 (32.9)	.0208
TIBC§, μg/dL (SD)	371.3 (33.2)	369.4 (22.3)	374.0 (45.9)	.9514	334.3 (34.0)	<.0001
Iron/TIBC§, % (SD)	24.5 (7.1)	22.3 (6.9)	27.5 (6.7)	.1087	34.1 (11.1)	.0013
Ferritin, ng/mL (SD)	17.1 (6.9)	18.8 (5.8)	14.6 (7.9)	.2448	52.4 (25.8)	<.0001

*Comparison of blood biochemical values between male and female participants

†Comparison of blood biochemical values for total participants at baseline and at 3 months

‡One patient refused blood test only at three months after oral iron administration.

§Abbreviations: Hb, hemoglobin; MCV, mean corpuscular volume; TIBC, total iron binding capacity

ng/mL decrease, 95% confidence interval 1.00 to 1.38; P = .0495).

School Attendance

During the study period, four participants normally attended school, including the one who attended kindergarten. Among the remaining 14 participants, nine did not attend school at all (MSAS score of 3). At week 12 of iron administration, school attendance worsened for one participant, remained unchanged for one, and improved minimally to very much for the remaining 12. The mean score (SD) of MSAS for the 14 participants at baseline was 2.3 (1.1), decreasing to 1.3 (1.1) at week 12 (P = .0122).

Discussion

We found that iron administration in children and adolescents with hypoferritinemia (<30 ng/mL) can improve symptoms such as anxiety, depression, poor concentration, irritability, low energy, fatigability, and/or insomnia, as well as CGI-S. Our results also suggested that iron administration for 12 weeks may improve school attendance, to varying degrees.

The current study showed the most prevalent physical symptoms resulting from hypoferritinemia were fatigability and insomnia, which influenced performance and activities of children during the daytime. Although these symptoms are also observed in RLS[7], only one case with RLS was confirmed in the current study, and none in our previous study[11]. Accordingly, iron administration should be considered when insomnia is noted in children and adolescents with hypoferritinemia, regardless of the presence of RLS.

In this study, the diagnoses of the participants varied. In addition, CGI and affective profiles according to POMS and CES-D showed moderate to severe values. Iron is not only used for Hb synthesis but also for the regulation of neurotransmitters such as dopamine and serotonin, acting as a cofactor in their production[29,30]. These mechanisms may underlie the results observed in this study. In addition, fatigability and insomnia caused by chronic hypoferritinemia may have induced a state that is predisposed to having anxiety, depression, irritability, poor concentration, and/or low energy. Furthermore, in participants with lower resilience to stress, fatigability and insomnia caused by chronic hypoferritinemia may have triggered a further decrease in resilience, thereby enhancing these psychiatric symptoms. Administration of oral iron could be considered for at least 12 weeks, regardless of diagnosis or gender, if the child or adolescent presents with these psychological and physical symptoms with hypoferritinemia. Incidentally, we found that six weeks of iron administration were insufficient to improve these outcomes[11].

The CGI-I score of the participant with major depressive disorder was significantly higher than that of other diagnoses, although only two participants had major depressive disorder. This result suggests that iron administration in children and adolescents with hypoferritinemia may not be as effective in those with major psychiatric disorders. Iron administration may reduce some symptoms of major psychiatric disorders; however, it does not directly help to improve those disorders.

In this study, no participants had anemia; therefore, Hb and MCV are not useful markers for detecting hypoferritinemia. Along with serum ferritin, serum iron, serum TIBC, and iron/TIBC significantly improved at week 12. Serum ferritin levels were significantly reduced in children who visit community mental health clinics[31]. Considering the current and our previous study[11], iron administration for hypoferritinemia-related psychological symptoms could be recommended when children and adolescents with physical and psychological symptoms described above have reduced serum ferritin levels <50 ng/mL[11], and it could be a better option for clinicians in cases where serum ferritin concentration is <30 ng/mL. In the present study, more than 50% of participants had physical symptoms such as dark circles under the eyes and the desire to eat something cold. Those symptoms may help detect hyooferritinemia in children who visit psychiatric and/or pediatric outpatient clinics.

In Japan, truancy has been increasing, while the number of students has been decreasing, leading to a potentially serious social issue. In 1991, the prevalence of absence was 1.04% in junior high schools and 0.14% in elementary schools[32]. However, in 2019, the prevalence had increased to 3.94% in junior high schools and 0.83% in elementary schools with the total number of absentees in junior high and elementary schools being the largest since 1991[33]. In this study, 74% of participants did not always attend school, and 47% did not attend school at all. However, at week 12 of iron administration, school attendance improved to varying degrees. Although the scale used in this study to assess school attendance (i.e., MSAS) has not been validated, these results might serve as a useful reference. Administering oral iron might be a better option for clinicians to truant students with reduced serum ferritin.

This study has the following limitations. First, this was

an open-label study. While the effect on ferritin is proven, and given the wealth of evidence linking improved hypoferritinemia to iron supplementation, the effect on symptom improvement observed in this study could have been due to a placebo effect. Randomized controlled trials should be conducted using the framework of hypoferritinemia. Second, the self-rating scales used in this study were not targeted toward children or adolescents aged 6-15 years. As such, each scale was evaluated through collaboration between the participant and the parent, resulting in self- and other-reported evaluations. Third, it was difficult to evaluate school attendance; therefore, we originally set the MSAS questionnaire. However, there is no data regarding the reliability and validity of this questionnaire. Fourth, all the patients were treated with usual psychotherapy in addition to oral iron therapy. Although inconsistent psycho-social therapy might have affected the results of iron therapy, special psycho-social therapies were not conducted to fully evaluate the effect of iron supplementation. Finally, the planned sample size was 25; however, the study was stopped after enrollment of 20 participants due to changes in the regulatory framework of clinical trials in Japan during the study period[34]. Because this was an exploratory study, we stopped further enrollment of participants and analyzed the data that had been collected.

Conclusions

Our findings suggested the importance of measuring serum ferritin levels in children and adolescents with insomnia and/or fatigability who visit psychiatric outpatient clinics, regardless of diagnoses or gender. Iron administration in children and adolescents with hypoferritinemia can improve psychological symptoms such as anxiety, depression, irritability, poor concentration, and/or low energy, which consequently might lead to a better quality of life. Clinicians working with children and adolescents could consider iron administration of at least 12 weeks for hypoferritinemia-related psychological symptoms, even if the child is not considered anemic.

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