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Prevalence of Iron Deficiency in Children with Down Syndrome

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Abstract

Objectives—To determine the prevalence of iron deficiency (ID) and iron deficiency anemia (IDA) in a sample of children with Down syndrome (DS) and to evaluate the effect of macrocytosis on the diagnosis of ID/IDA in these children.

Study design—Children with DS ≥ 12 months of age who were followed at the Duke University Medical Center Comprehensive DS Clinic from December 2004 to March 2007 were screened for ID/IDA with a complete blood count (CBC), reticulocyte count, iron panel and erythrocytic protoporphyrins.

Results—114 children were enrolled, with a median age of 4.7 years. ID was identified in 12 (10%) and IDA in 3 (3%) subjects. ID/IDA would not have been accurately diagnosed in 13 of 15 (86%) subjects if red blood cell (RBC) indices alone had been used for screening. Abnormal RBC indices together with low transferrin saturation (TS) were 100% sensitive for ID/ IDA screening.

Conclusions—Prevalence of ID/IDA among children with DS was comparable with the general pediatric population. Macrocytosis had implications for screening of ID/IDA using only RBC indices. We suggest ID/IDA screening in DS children to be done using a laboratory panel at least including CBC, reticulocyte count, TS, and serum ferritin.

Keywords

Iron deficiency anemia; macrocytosis; hematologic indices

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In the United States, there are thought to be approximately 400,000 people with Down syndrome (DS) (1,2). Screening, identification, and prompt treatment of underlying medical issues such as hypothyroidism in infants with DS, can significantly improve medical and cognitive outcomes.

Elevation of the red blood cell (RBC) indices is frequently encountered in patients with DS (3–7). Elevated RBC mean corpuscular volume (MCV) or macrocytosis is reported to occur in 45% to 66% of such children (5,8). The etiology of the macrocytosis unknown and not related to vitamin B12 deficiency, folate deficiency, increased fetal hemoglobin concentration, reticulocytosis, or hypothyroidism (3,9–11).

Iron deficiency anemia (IDA) affects not just hematopoiesis, but the function of other organ systems, including the nervous system (12). IDA has been associated with neurocognitive disabilities (13–15) and stroke (16). There is evidence suggesting that cognitive or behavioral performance and brain function could be affected by iron deficiency (ID), particularly if deficiency occurs during critical stages of development (17). In recent publications, it has been postulated that ID could be considered a risk factor associated with attention-deficit/hyperactivity disorder (ADHD) (18,19), pediatric restless legs syndrome (RLS) and sleep disturbances in children with ADHD (20–22) and children with periodic limb movements in sleep (PLMS) (21,23). The diagnosis of subclinical ID before anemia develops is of great importance because earlier diagnosis would allow for timely replacement of iron and prevention of progression of hematologic and neurocognitive effects of IDA.

The prevalence of ID in children with DS is not well characterized. Current health supervision guidelines for children with DS recommend obtaining a complete blood count (CBC) in the newborn period and annually between ages of 13 and 21 years (24). Recommendations for screening for ID/IDA in children with DS are based on those for children in the general population; this includes that hemoglobin (or hematocrit) be checked initially between the ages of 9 to 12 months. Additional screening between the ages of 1 and 5 years is suggested for patients at risk to develop ID/IDA. The screening may be universal or selective depending on the prevalence of IDA in the population. The validity of this method for screening for ID has been questioned because anemia is the last stage to develop even when significant ID is present. Most children with ID are not anemic at the time of routine screening, thus many toddlers who might benefit from iron therapy are not provided appropriate treatment (25).

Here, we report the results of a single-center, prospective study of 114 children and adolescents with DS to determine the prevalence of ID/IDA in a clinic convenience sample. We hypothesized that the presence of ID and IDA in DS may be underestimated using typical screening because macrocytosis in children with DS may be falsely reassuring of adequate iron stores.

Methods

This study was a single center, prospective observational study. The research protocol was approved by the DUMC Institutional Review Board. The project was conducted between December 2004 and March 2007 in the DUMC Comprehensive DS Clinic. About 400 patients are followed in the Clinic annually. Inclusion criteria required subjects to be ≥12 months with a clinical diagnosis of DS.

All patients ≥12 months followed in the DUMC Comprehensive DS Clinic were routinely screened for ID/IDA by obtaining a CBC, reticulocyte count, peripheral blood smear, serum ferritin concentration, serum iron (SI), total iron binding capacity (TIBC), free erythrocytic

protoporphyrin (FEP), and zinc complex protoporphyrin (ZCP) concentrations, and by calculating the transferring saturation (TS).

The blood samples (minimum 8 mL) were collected by venipuncture, and processed by the DUMC medical laboratories according to their established standard procedures.

Patients diagnosed with ID or IDA were given oral iron at a dose of 4–6 mg/kg/day of elemental iron to be taken for four months with follow-up arranged either with the child's primary care provider (PCP) or at the Clinic using the same laboratory measures. Children found to have ID/IDA were provided with guaiac cards to test for fecal blood loss. For individuals found to have an elevated FEP or ZCP, lead levels were obtained upon follow up in the clinic or by requesting this information from the PCP.

After written informed consent was obtained from the parents or legal guardians we collected demographic, clinical and laboratory data from the medical records of children enrolled in the study. Peripheral smears of enrolled subjects were also examined by a pediatric hematologist [ND].

Definitions

ID was defined as: (1)

Two or more abnormal biochemical markers of iron (low serum ferritin concentration, low TS, elevated FEP or elevated ZCP); or (2) one abnormal biochemical marker of iron plus an elevated RDW.

IDA was defined as:

(1) ID (see above); and (2) a low hemoglobin concentration, defined as below two SD below the mean for age and sex.

Statistical analyses

Comparisons between groups were made using Fisher exact tests or Kruskall-Wallace test where appropriate. Receiver operating curve (ROC) was used to determine the relative diagnostic utility of the biochemical measures and RBC indices used to diagnose ID/IDA. The sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV), were calculated based on commonly accepted diagnostic cutoff values for children. Analyses were conducted using STATA 10 (College Station, Texas).

Results

The median age of the 114 subjects enrolled was 4.7 years (range 1.0 to 19.7). Overall, 52 subjects (46%) were females; 75 (66%) were white, 21 (18%) Black, 17 (15%) Hispanic, and 1 (1%) Asian. Of the 114 subjects, 12 (10.5%) had ID and three (2.6 %) had IDA. No significant demographic differences were identified between the three groups (Table I).

Results of hematologic indices by iron status are presented as the mean ± SD (Table II) and biochemical indicators by iron status are presented as the mean ± SD (Table III; available at www.jpeds.com). Normal hematologic values as well as serum ferritin, SI and TS change with age; therefore for this analysis the subjects were divided into two age groups, 12 to 36 months and > 36 months.

The diagnostic utility of individual tests and combination of different tests to screen for ID/IDA is presented in Tables IV and V. The ROC of low TS was 0.91. The combination of

abnormal RBC indices (MCV, MCH, MCHC and RDW) along with a low percentage of TS was 100% sensitive and had a NPV of 100% for identifying patients with ID/IDA.

Our sample showed an overall prevalence of macrocytosis adjusted for age of 22%; when our cohort was divided by age groups the prevalence was as follows: one to less than six years of age (33%), more than six to less than twelve years of age (14%) and older than twelve years of age (4%).

Forty-one subjects had elevated FEP or ZCP, and 14/41 (34%) had ID or IDA; the remaining 27 (66%) did not fulfill criteria for ID/ IDA. Lead levels were obtained on 25 of 41 subjects with elevated FEP or ZCP concentrations. All were within normal limits including five from subjects with ID/IDA.

Clear morphological changes in the RBC consistent with ID/IDA were only seen in the 3 patients who were diagnosed with IDA. None of the subjects had findings suggestive of folic acid or vitamin B12 deficiency. Findings typically seen in the peripheral blood smear of megaloblastic anemia include numerous macro-ovalocytes as well as schistocytes of various sizes and spherocytes (because of increased fragility of these erythrocytes). Hypersegmentation of mature neutrophils is a characteristic feature that appears very early in the development of megaloblastic anemia reflecting nuclear maturation defect.

Discussion

We report the prevalence of ID and IDA in a convenience sample of children and adolescents with DS recruited from a DS Clinic. The prevalence of ID (10.5%) and IDA (2.6%) in our sample is comparable with that found in the general pediatric population reported in the NHANES III study from 1988 to 1994 (26). We did not find any statistically significant difference in the distribution of ID among children with DS with respect to sex or ethnicity compared with the unaffected/iron replete children

Only 2 of the 114 subjects had a MCV result that was below the normal range for age, and both of those patients had clear IDA. Aside from those two subjects, the distribution of MCV values overlapped between the normal, ID and IDA groups. In our cohort a low MCV and low MCH individually had poor sensitivity for screening of ID/IDA consistent with our hypothesis. Even when examined in combination with other RBC indices (MCV, MCH, MCHC, and RDW), the sensitivity was unacceptably low at 61%. Therefore, our data indicates that the macrocytosis of DS can mask the diagnosis of ID/IDA, confirming the suggestion by Starc (5).

The NPV is the probability that the disease is not present when the test is negative and **t**he area under the ROC curve determines the ability of a test to discriminate between subjects with the disease from those without the disease (tests with areas > 0.9 generally considered excellent and those with areas between 0.8 and 0.9 considered good). In our study, the ROC of low TS was 0.91; the combination of abnormal RBC indices (MCV, MCH, MCHC and RDW) along with low TS was 100% sensitive and had a NPV of 100% for identifying patients with ID/ IDA. Adding serum ferritin concentration, FEP and ZCP had little utility in increasing the sensitivity or NPV of the screening panel. We found that low TS was the best individual screening predictor of whether or not a patient had ID/IDA.

We still recommend obtaining a CBC and reticulocyte count at diagnosis and subsequent follow up after iron replacement has been initiated not only to determine response to therapy but also to establish the true baseline of these RBC indices for the individual patient. Serum ferritin concentration as a sole indicator of iron depletion was not sensitive enough for screening of ID/IDA in our sample. However a low serum ferritin is an important diagnostic clinical tool confirming iron depletion when used in combination with other measurements of iron status.

Iron supplementation should be administered until there is no evidence of iron depletion, which usually requires at least 4–6 months of therapy or the individual will eventually progress again into a state of ID/IDA.

Patients who are followed by the DUMC Comprehensive DS Clinic are routinely screened for thyroid disorders and treated accordingly. Patients with a history of thyroid dysfunction were on proper treatment at the time of phlebotomy. None of the peripheral blood smears had findings suggestive of folic acid or vitamin B12 deficiency. We conclude that hypothyroidism or megaloblastic anemia were not a likely explanation for the increased RBC indices including the MCV among our study sample. These findings are consistent with the findings in patients with DS from prior published studies (3,10).

Clear morphological changes in the RBC were only seen in the 3 patients who were diagnosed with IDA, therefore review of the peripheral blood smear was of low utility for screening for ID in this sample. Based on this finding and given that this diagnostic tool requires special expertise and is not usually available in the primary care setting we do not recommend its routine use for screening of ID. However evaluation of the peripheral blood smear continues to be essential for the assessment of anemia not explained by ID or for other worrisome findings in the CBC, especially given the increased risk to develop myelodysplastic syndrome and leukemia among individuals with DS.

Our findings confirm that the underlying macrocytosis of DS can mask a diagnosis of ID and a more thorough laboratory evaluation should be done for screening of ID among these patients. Thirteen out of 15 subjects with ID/IDA would have been missed if we had solely used the standard hemoglobin or MCV that is currently recommended for typically developing children. With this study we suggest that when children with DS are screened for ID/IDA, an expanded laboratory panel should be used, including a CBC, reticulocyte count, serum iron, TIBC, and serum ferritin concentration.

Sufficient iron stores are of great importance to maximize learning and psychomotor development, particularly in children with baseline cognitive delay as in DS. We recommend that baseline screening tests be done between 9 to 12 months of age and annually when children with DS are thought to be at risk for ID/IDA. Other associated conditions that might make children with DS prone for ID/IDA are: surgical interventions in the 1st year of life; feeding problems (hypersensitivity and/or food selectivity); history of menorrhagia; gastro esophageal reflux disease and history of Celiac disease. Macrocytosis among patients with DS has been found with variable frequency (45–66%). In our study, 22% of the total subjects had macrocytosis; this difference in frequency compared with other published data can be due to the number of subjects studied as our cohort is larger than of the previously reported. In our sample macrocytosis was found more frequently among the young children (33% of subjects one to less than six years of age); this finding also supports our recommendation to screen children with DS with an extended panel of laboratory tests early in life when macrocytosis can mask more individuals with ID/IDA, especially given that younger children could be more susceptible to non reversible neuro-cognitive effects related to prolonged IDA when compared with older peers.

A limitation to our study is that we did not use a "gold standard" to diagnosis ID. Gold standard for the diagnosis of ID includes a bone marrow biopsy stained by Prussian Blue for iron stores. Given the invasiveness of obtaining a bone marrow specimen, evaluation of the improvement in the hemoglobin concentration, RBC indices, reticulocyte count and biochemical measures of ID is typically used to assess the response to iron treatment. We encountered difficulties when bringing the subjects back to the DS Comprehensive Clinic or the PCP office for repeated

laboratory evaluation after iron therapy, only few of them accomplished this goal, not enough for meaningful comparisons.

ID is an unrecognized problem among children with DS and the effects of ID on this population remain to be studied. A larger, community-based study of ID/IDA in individuals with DS should be done before further screening recommendations are made.

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List of abbreviations

DS	Down syndrome
ID	Iron deficiency
IDA	Iron deficiency anemia
CBC	Complete blood count
RBC	Red blood cells
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
RDW	Red blood cell distribution width
Hgb	Hemoglobin
SI	Serum iron
TIBC	Total iron binding capacity
TS	Transferrin saturation
FEP	Free erythrocytic protoporphyrin
ZCP	Zinc complex protoporphyrin
ADHD	Attention-deficit/hyperactivity disorder
RLS	Restless leg syndrome
PLMS	Periodic limb movements in sleep
ROC	Receiver operating curve
NPV	Negative predictive value
PPV	Positive predictive value

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Table I

Demographic characteristics among children with DS by iron status

	Normal (N = 99)	ID (N = 12)	IDA (N = 3)	P
Sex				
Female	45 (45%)	6 (50%)	1 (33%)	0.91
Male	54 (55%)	6 (50%)	2 (67%)	
Ethnicity				
Caucasian	66 (67%)	9 (75%)	0 (0%)	0.11
Black	19 (19%)	1 (8%)	1 (33%)	
Hispanic	13 (13%)	2 (17%)	2 (67%)	
Asian	1 (1%)	0 (0%)	0 (0%)	
Age				
12–36 months	N = 32	N = 8	N = 2	
> 36 months	N = 67	N = 4	N = 1	
Mean (year) ± SD	6.8 ± 5.1	4.9 ± 5.7	4 ± 2.5	
Median (year)	4.9	1.7	3	0.11

Abbreviations defined in text

Table II

Hematological findings among children with DS by iron status

	Normal	ID	IDA
Hgb (g/dL)			
12–36 months	13.1 ± 1.1 (N=31)	12.6 ± 0.8 (N=7)	11.3 ± 0.0 (N=2)
> 36 months	13.8 ± 1.0 (N=67)	14.1 ± 1.3 (N=4)	10.5 (N=1)
MCV (fl)			
12–36 months	85.2 ± 3.6 (N=31)	82.8 ± 4.3 (N=6)	74.5 ± 19.1 (N=2)
> 36 months	89.6 ± 5.0 (N=67)	89.2 ± 3.3 (N=4)	69 (N=1)
MCH (pg)			
12–36 months	29.2 ± 1.5 (N=30)	28 ± 1.9 (N=6)	24.7 ± 8.2 (N=2)
> 36 months	30.7 ± 1.8 (N=65)	30.3 ± 1.30 (N=4)	21.6 (N=1)
MCHC (%)			
12–36 months	34.2 ± 0.8 (N=31)	33.8 ± 1.0 (N=6)	32.9 ± 2.6 (N=2)
> 36 months	34.4 ± 1.1 (N=67)	34.0 ± 1.6 (N=4)	31.3 (N=1)
RDW (%)			
12–36 months	14.1 ± 1.3 (N=31)	14.5 ± 0.9 (N=6)	18.1 ± 2.6 (N=2)
> 36 months	13.4 ± 0.8 (N=67)	14.3 ± 0.6 (N=4)	17.1 (N=1)

Abbreviations defined in text

Table III

Iron related biochemical findings among children with DS by iron status

	Normal	ID	IDA
TS (%)			
12–36 months	23.1 ± 11.9 (N=28)	10.4 ± 3.2 (N=8)	7.5 ± 2.1 (N=2)
> 36 months	22.0 ± 7.5 (N=64)	13.7 ± 0.5 (N=4)	4.0 (N=1)
Ferritin (ng/mL)			
12–36 months	43.2 ± 28.3 (N=31)	31.3 ± 19.2 (N=6)	8.0 ± 4.2 (N=2)
> 36 months	61.2 ± 44.6 (N=64)	44.5 ± 37.2 (N=4)	5.0 (N=1)
FEP(μg/dL)			
12–36 months	10.7 ± 7.4 (N=24)	15.7 ± 10.1 (N=8)	54.5 ± 13.4 (N=2)
> 36 months	8.6 ± 5.4 (N=60)	15.2 ± 4.0 (N=4)	-
ZCP (μg/dL)			
12–36 months	38.6 ± 12.4 (N=24)	45.4 ± 16.0 (N=8)	99 ± 69.3 (N=2)
> 36 months	31.7 ± 13.1 (N=60)	47.2 ± 14.9 (N=4)	-

Abbreviations defined in text

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Table IV

Diagnostic utility of individual tests for ID/IDA % [95% Confidence Interval]

	Sensitivity	Specificity	PPV	NPV	ROC
Low MCV	15 [2, 45]	100 [96, 100]	100 [16, 100]	90 [83, 95]	0.68
Low MCH	15 [2, 45]	100 [96, 100]	100 [16, 100]	90 [82, 95]	0.71
High RDW	62 [32, 86]	87 [78, 93]	38 [18, 62]	94 [88, 98]	0.82
Low Ferritin	23 [5, 54]	100 [96, 100]	100 [29, 100]	90 [83, 95]	0.75
Low TS saturation	100 [78, 100]	85 [76, 91]	52 [32, 71]	100 [95, 100]	0.91
High FEP	86 [57, 98]	77 [67, 86]	39 [22, 58]	97 [90, 100]	0.81
High ZCP	79 [49, 95]	74 [63, 83]	33 [18, 52]	95 [87, 99]	0.81

Abbreviations defined in text

Table V

Diagnostic utility of screening panels for ID/IDA (at least 1 positive value) % [95% Confidence Interval]

	Sensitivity	Specificity	PPV	NPV
RBC Indices*	61 [32, 86]	87 [78, 93]	38 [18, 62]	94 [88, 98]
RBC Indices*, Ferritin	60 [32, 84]	87 [79, 93]	41 [21, 64]	94 [86, 98]
RBC Indices*, TS	100 [78, 100]	77 [67, 85]	40 [25, 57]	100 [95, 100]
RBC Indices*, TS, Ferritin	100 [78, 100]	77 [67, 85]	40 [24, 57]	100 [95, 100]
RBC Indices*, TS, Ferritin, FEP	100 [78, 100]	61 [50, 70]	28 [16, 42]	100 [94, 100]

* RBC indices refers to MCV, MCHC, MCH, and RDW

Other abbreviations defined in text