

Characterization of Pica Prevalence Among Patients With Sickle Cell Disease

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Objective: To determine the prevalence of pica and its characteristics among children with sickle cell disease.

Design: Retrospective, observational study.

Setting: An urban, ambulatory care, interdisciplinary center.

Patients: The medical records of all 480 patients who visited the center from March 1, 1998, to June 30, 1999, were reviewed. Patients were excluded for history of stroke, long-term transfusions, pregnancy, acute illness, or age younger than 3 years.

Main Outcome Measures: Sex, age, weight, height, Tanner stage, complete blood cell count, sickle cell genotype, pica history, and levels of iron, zinc, lead, and fetal hemoglobin (Hb).

Results: Of 395 study patients, 134 (33.9%) reported pica. Ingested items included paper, foam, and powders. There was a significantly higher prevalence of pica

among patients homozygous for Hb S (Hb SS, sickle cell anemia) compared with the combined group of double heterozygous patients with Hb SC, Hb SD, and Hb S β thalassemia (S β ⁺ or S β ⁰) (35.6% vs 25.5%; $P = .03$). Within genotype, mean Hb levels were significantly lower and reticulocyte counts were significantly higher in the patients with pica. Overall, the mean age of patients with pica was significantly lower; however, the prevalence was 23.3% (27/116) among those aged 10.0 to 14.9 years and 14.8% (8/54) among those aged 15.0 to 19.0 years. Within age groups, patients with pica weighed significantly less.

Conclusions: Pica appeared to have an unusually high prevalence in patients with sickle cell disease and a correlation with lower Hb levels. It is unclear whether pica is a specific marker of disease severity, because our review did not show a relationship to increased number and duration of hospitalizations. The association between pica and low body weight suggests a nutritional effect on its prevalence.

Arch Pediatr Adolesc Med. 2001;155:1243-1247

PICA IS THE compulsive ingestion of particular food items or nonnutritive substances. This unusual behavior may lead to a variety of complications, including abdominal complaints, poisoning, electrolyte imbalance, and dental injury. Although the etiology is poorly understood, associations have been described with iron deficiency, zinc deficiency, mental and developmental delay, psychosocial problems, and family history of pica.¹⁻³

Pica has been classically associated with iron deficiency and lead encephalopathy. Among the many groups experiencing pica are pregnant women; in 1 study, 56% of the women surveyed reported regular ingestion of dirt (geophagia). In this group, the average hemoglobin (Hb) and ferritin levels were below the reference range.⁴ Zinc deficiency has also been considered as a cause for pica. A study of 213 preschool children with low zinc levels, assessed by means of hair sampling, showed pica to be a frequent presenting com-

plaint. Subsequent zinc supplementation resulted in elimination of pica.⁵ Patients exhibiting pica have been shown to have decreased iron and zinc absorption, compared with control subjects.⁶ Although a causal effect has not been determined, several other studies have also reported improvement of pica with zinc supplementation.^{7,8} Pica has been specifically described in children with sickle cell disease (SCD). In a previous questionnaire study from our institution, 170 patients with SCD were observed and a significant proportion (33.5%) of the patients reported having pica.⁹

To examine the factors associated with this unusually high prevalence of pica in SCD, we reviewed all routine visits (480 patients) during a 15-month interval (March 1, 1998, through June 30, 1999) and tested the following 3 hypotheses. First, pica occurs in children with SCD at an unusually high prevalence and at an older age than has been previously described in other populations. Second, pica is an indicator of disease severity, reflected by the number of hospitalizations

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SUBJECTS AND METHODS

SUBJECT SELECTION

All patients with SCD enrolled in the Sickle Cell Center at Children's Hospital of Michigan, Detroit, were eligible for this study. The diagnosis of the genotype was confirmed using results of Hb electrophoresis and quantitation of HbA₂ by means of column chromatography and fetal Hb (Hb F) by means of acid elution. Clinical information obtained during each routine visit to the Sickle Cell Center included a history form with a specific question inquiring about pica behavior. If pica was reported, the items ingested were also noted on the form. For purposes of the study, all Sickle Cell Center history forms were reviewed for patients presenting for routine visits during the 15-month study period. Most patients had more than 1 routine visit during the study period. Patients (and/or their caregivers) reporting pica at any visit during the study period were categorized as pica. Patients denying pica at all visits during the study period were categorized as nonpica.

EXCLUSION CRITERIA

Patients were excluded from the study if they were younger than 3 years, were pregnant during the study period, or had an affirmative response for pica but the detailed notes reported a behavior that did not constitute pica (eg, nail-biting). In addition, any patient known to have a profound mental handicap unrelated to SCD (eg, cerebral palsy), was excluded from the study.

Of the 480 patients who had routine visits during the study period, 36 were excluded for age younger than 3 years, 16 were excluded for undetermined pica status, and 1 patient was excluded for severe mental deficiency unrelated to SCD. The 6 patients with Sβ⁰ or Hb SD (n=5 and n=1, respectively) were not included in the statistical analysis. Although many patients received occasional blood transfusions, patients who sustained a stroke as a complication of SCD received long-term transfusions. For this reason, the 26 patients in this category during the study period were analyzed as a separate group. The final analysis was performed in 395 patients who fit study criteria.

DATA COLLECTION

For 169 study patients, laboratory values were obtained from the clinic's computer database for Hb, hematocrit, mean corpuscular volume, and reticulocyte count. If more than 1 set of values were obtained within the study period, an average value was reported. If the patient's values were not available from the database, they were obtained directly from their medical record (n=226). In these cases, a single steady-state observation was used. On rare occasions, the laboratory report for the date of visit was missing. In those situations, the next closest steady-state blood sample drawn within the study period was used.

Values for weight, height, Tanner stage, red blood cell count (RBC), and Hb F level were obtained from the

medical records for all pica patients. These values were also recorded for an unselected sample of nonpica patients for whom these data were available (n=91). Some patient information forms reported a different Tanner stage between breast development and genital development. For these patients, the average of both stages was reported. Also, for patients whose Tanner stage progressed during the study period, the average of the Tanner ratings was reported.

Data regarding numbers of hospitalizations and days in hospital were obtained from the inpatient hospital medical record database for the entire study period, including all patients with a diagnosis of SCD crisis (using the *International Classification of Diseases, Ninth Revision*, code). In a few instances, the history form indicated hospitalizations at outside institutions, and this information was also included in our analysis. Study age was calculated at the date of first visit during the study period. Weight and height percentiles were determined based on standardized growth charts published by the National Center for Health Statistics, Hyattsville, Md.

An insufficient number of patients (n=10) underwent testing for levels of iron, zinc, or lead to draw any meaningful conclusions. Four patients who had visits during the study period were excluded from the analysis of laboratory values because of missing laboratory records.

EXTREME VALUES

In the data analysis, all extreme laboratory values (beyond 2 SDs above or below the mean) were individually reviewed to confirm their accuracy. Some of these values were obtained from patients who were ill at the visit in question, and therefore their laboratory data did not represent a steady-state value. For these patients, the next closest well-patient visit was used for laboratory values.

STATISTICAL METHODS

Comparisons of associations between categorical variables were performed using the Fisher exact test, with differences in proportions considered statistically significant at $P \leq .05$ (2-tailed). Although the Fisher exact test is most commonly known for applications with small-sample data sets, it is a permutation test. This avoids the possibility of misinterpretation of statistical significance using asymptotic test results. Differences in mean values within specific genotype groups by pica presence or absence were conducted using the independent samples *t* test. Appropriate assumptions (eg, normality and homogeneity of variance) were checked and verified. Exploratory data analysis procedures were conducted to examine the data for outliers and extreme values. Two-factor analysis of variance (ANOVA) procedures were performed to examine mean differences in continuous, dependent variables using pica status (presence or absence) and age group category (3.0-4.9, 5.0-9.9, 10.0-14.9, and 15.0-19.0 years) as factor variables. Again, appropriate assumptions were checked and verified. Differences in mean values were considered statistically significant at $P \leq .05$.

and days spent in the hospital. Finally, there is a higher prevalence of pica (as a marker of impaired mental development) among patients with SCD who have a complication of stroke when compared with the general population with SCD.

The aims of our study were to determine the prevalence of pica in SCD patients by self report and/or report from caregivers; to assess the age and sex distribution among the pica patients compared with their nonpica counterparts; to compare laboratory values for patients

with and without pica; to compare hospitalization rates and number of days in hospital for patients with and without pica; and to study the prevalence of pica among patients with SCD complicated by stroke.

RESULTS

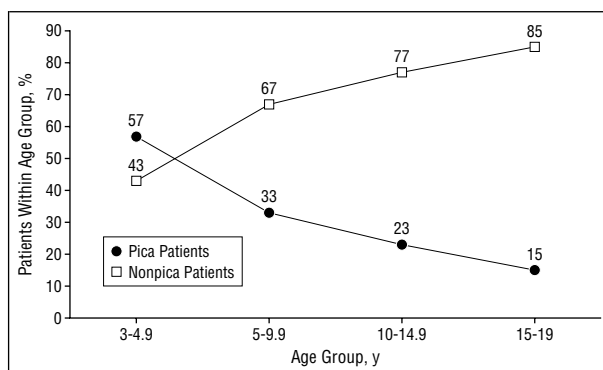
Of the 395 study patients with SCD and the genotypes for Hb SS, Hb SC, or Hb Sβ⁺, 125 (31.6%) responded affirmatively to the question of pica. Parents reported repeated ingestion of nonfood items. Some parents reported changing purchasing practices (eg, discontinuing daily newspaper delivery) in an attempt to stop or control their child's ingestion pattern. Other anecdotal examples included finding large areas of missing foam in sofa seat cushions, which had been eaten by the child. The types of nonfood items ingested by patients covered a broad spectrum, as seen in the following tabulation (with some patients reporting ingestion of more than 1 type of item):

Item	No. of Patients
Paper (cardboard, paper, paper towels, tissue paper, toilet paper)	37
Fabric (bedding, clothing, carpeting, string)	21
Dirt	7
Foam (cushion foam, sponge, styrofoam)	7
Powder (cleansers, ashes, baby powder)	5
Pencils	2
Cotton	1
Crayons	1
Erasers	1
Hair	1
Paint	1
Popsicle sticks	1
Soap	1
Toys	1
Fabric closures (Velcro)	1

The pica patients were strikingly similar by sex, with 62 (49.6%) of 125 female and 63 (50.4%) male. When considering pica prevalence within SCD genotype, a larger percentage of patients had pica in the Hb SS group (85/238 [35.7%]) compared with the combined Hb SC/Sβ⁺ group (40/157 [25.5%]; $\chi^2=4.58$; $P=.03$).

Overall, mean ages were significantly lower for children with pica than for those without pica (7.9 ± 3.7 vs 10.1 ± 4.0 years; $t=-5.21$; $P \leq .001$). Similarly, mean ages in the pica and nonpica groups differed within SCD genotype groups. The pica patients in the Hb SS group were an average of 1.9 years younger than their nonpica counterparts (8.5 vs 10.4 years; $t=-3.51$; $P \leq .001$). Those in the Hb SC/Sβ⁺ group were an average of 3.1 years younger (6.6 vs 9.7 years; $t=-4.57$; $P \leq .001$). To further examine the influence of age on the prevalence of pica, patients were grouped into 4 age categories (3.0-4.9, 5.0-9.9, 10.0-14.9, and 15.0-19.0 years). Analyses were conducted by combining genotype groups ($n=395$). The prevalence of pica was found to be inversely associated with age (**Figure**). As age increased, the prevalence of pica within each age category decreased (χ^2 test for trend, 29.38; $P \leq .001$).

Mean differences in laboratory values between children with pica vs those without pica were examined



Relationship between pica and age.

($n=395$). Overall mean RBC and body weight values were all significantly lower ($P \leq .001$) for pica patients than for the nonpica patients.

Within specific genotype (**Table 1**), the mean Hb level in the pica group was found to be significantly lower than that of nonpica patients in the Hb SS group (7.6 ± 1.0 vs 8.2 ± 1.1 g/dL; $t=-3.86$; $P < .001$) and approached significance in the Hb SC/Sβ⁺ group (10.7 ± 1.3 vs 11.1 ± 1.1 g/dL; $t=-1.84$; $P=.07$). Mean reticulocyte counts were higher in pica patients with both genotypes compared with nonpica patients. This difference did not reach statistical significance. Analysis of mean RBC, mean corpuscular volume, and Hb F values did not show statistically significant differences in genotype groups.

Given that weight and height increase with age, we conducted a 2-factor ANOVA to examine differences within specific age category by pica type for genotype groups. The mean weights in each age category for both genotype groups taken together were lower for patients identified with pica through 15 years of age. This difference was statistically significant for patients aged 5.0 to 9.9 years (**Table 2**). In the Hb SS group, the largest mean difference in weight occurred in patients aged 5.0 to 9.9 years, where pica patients had a significantly lower mean weight than nonpica patients (23.3 ± 1.6 vs 30.2 ± 2.7 kg; $P=.05$). In the Hb SC/Sβ⁺ group, the largest mean difference in weight was in patients aged 10.0 to 14.9 years, where pica patients recorded a lower mean weight than nonpica patients (37.8 ± 4.1 vs 43.0 ± 1.9 kg; $P=.25$). The mean height in each age category for both genotype groups taken together was consistently lower for pica patients than for nonpica patients, through 10 years of age. These differences were not statistically significant (**Table 2**). In this age group, pica patients had a lower mean height (93.1 ± 4.7 cm) than nonpica patients (102.6 ± 11.1 cm; $P=.43$). In the Hb SC/Sβ⁺ group, the largest mean difference in height occurred in the group aged 5 to 9.9 years, where pica patients recorded a mean height significantly lower than that of nonpica patients (114.3 ± 4.0 vs 125.4 ± 3.4 cm; $P=.04$).

The mean number of days in the hospital during the study period did not vary significantly between the patients with and without pica (3.08 vs 3.21 ; $t=-0.19$; $P=.85$). Similarly, differences in the number of hospitalizations between groups for the study period were infinitesimal (0.762 for pica subjects vs 0.764 for nonpica subjects; $t=-0.01$; $P=.99$).

Table 1. Laboratory Values for Children Aged 3 to 19 Years*

	Hb SS Genotype			Hb SC/Sβ + Genotype		
	No. of Patients	Mean (SD)	P Value (2-Tailed)	No. of Patients	Mean (SD)	P Value (2-Tailed)
Hemoglobin level, g/dL						
Pica	84	7.6 (1.0)	<.001	39	10.7 (1.3)	.07
Nonpica	153	8.2 (1.1)		117	11.1 (1.1)	
Reticulocyte count, ×10 ³ /μL						
Pica	84	14.9 (4.8)	.08	39	4.1 (3.7)	.52
Nonpica	151	13.6 (5.7)		112	3.8 (2.2)	
RBC, ×10 ⁶ /μL						
Pica	84	2.7 (0.4)	.24	39	4.4 (0.7)	.36
Nonpica	31	2.8 (0.5)		57	4.5 (0.5)	
MCV						
Pica	84	84.0 (7.8)	.81	39	71.4 (6.9)	.44
Nonpica	153	84.3 (8.7)		117	72.4 (6.3)	
Fetal hemoglobin level, g/dL						
Pica	67	8.8 (7.6)	.63	31	4.8 (4.3)	.43
Nonpica	28	8.1 (5.0)		48	4.1 (4.3)	

*Laboratory data had occasional missing values. Hb indicates hemoglobin; RBC, red blood cell count; and MCV, mean corpuscular volume. Genotype abbreviations are explained in the "Results" section.

Table 2. Analysis by Age Groups*

Age, y	Weight, kg			Height, cm		
	No. of Patients	Mean (SE)	P Value	No. of Patients	Mean (SE)	P Value
3.0-4.9						
Pica	38	16.0 (1.5)	.44	38	95.3 (3.1)	.25
Nonpica	12	18.3 (2.6)		12	102.6 (5.7)	
5.0-9.9						
Pica	52	23.5 (1.3)	.03	52	115.0 (2.7)	.09
Nonpica	35	28.0 (1.6)		36	122.3 (3.3)	
10.0-14.9						
Pica	27	37.4 (1.8)	.07	28	142.2 (3.7)	.78
Nonpica	28	41.9 (1.8)		28	140.7 (3.7)	
15.0-19.0						
Pica	7	65.1 (3.5)	.02†	7	161.0 (7.5)	.86
Nonpica	12	54.6 (2.6)		13	162.7 (5.5)	

*Includes all genotypes and those patients for whom complete data were available on the appropriate visit dates.

†Results were skewed by several outliers in small sample size.

Twenty-six patients had had strokes and were receiving long-term transfusions for this complication. Of these, 9 patients (34.6%) had history of pica, which was not significantly different from the patients without stroke (125/395 [31.6%]).

COMMENT

Pica has been described in many different populations. It is generally agreed that "mouthing" is acceptable for children during the toddler years (≤ 18 months), when oral exploration of the child's environment is a part of normal behavior.¹⁰ However, the condition of pica seen in the SCD population goes beyond putting objects in one's mouth, or even incidental ingestion of such things. Pica in SCD patients appears to be a departure from normal development. Our study showed that in a sizable group of SCD patients, the average age for pica was 8.5 years.

Traditionally, pica has been related to iron deficiency or lead poisoning. Since this was a retrospective

study, we did not have sufficient data on lead or iron levels. The RBC indices in our patients were not hypochromic or microcytic and thus not suggestive of iron deficiency. Although iron deficiency has been described in SCD, it is not usually seen in older patients with sickle cell anemia. This could be explained by iron added via the sporadic transfusion of red blood cells often needed to manage complications of the disease. Iron deficiency is also unusual because the chronic underlying hemolysis of red blood cells results in reutilization of iron from the metabolized heme. Because the onset of puberty is reported to be delayed in SCD,¹¹ the lack of menstrual blood loss in female patients also lowers the risk for iron deficiency in this group.

Within each of the genotype groups, Hb and hematocrit levels were lower. In addition, the reticulocyte count was higher in pica patients with the Hb SS genotype, perhaps indicating a higher hemolytic rate when pica occurs. The significantly higher proportion of pica in patients with the Hb SS genotype vs those with Hb SC

What This Study Adds

Pica is the unusual compulsion to ingest nonfood substances, typically associated with iron deficiency and lead encephalopathy. It has been observed to be particularly prevalent among patients with sickle cell disease, although previous reports do not systematically describe its occurrence in this population.

This study determined that pica has an unusually high prevalence in patients with sickle cell disease and a correlation with worse anemia in the SS genotype. It may not be a marker of disease severity because it was not related to increased hospitalization. The association between pica and low body weight suggests a nutritional effect.

and Hb S β^+ thalassemia could be explained by the known worse disease severity in the former genotype. However, the analysis of days in hospital and number of hospitalizations in pica and nonpica patients did not disclose any significant differences, and thus pica may not be a specific marker of disease severity.

Our data show that patients with pica had lower average weights in all age groups, except for those older than 15 years. The differences were statistically significant in patients aged 5.0 to 9.9 years. These findings suggest a role for nutrition in the prevalence of pica. It is reasonable to consider that there are high caloric needs because of a hypermetabolic state secondary to chronic hemolysis in this disease. The inability to meet these higher energy demands may increase with age and the usual needs of growth. Whether pica was the cause of lower body weight or its effect was not answered by our data. The influence of age on pica was also important. Pica prevalence was the highest in the youngest patients, and there was a decrease in pica with increasing age. However, our prevalence of pica in older children (aged 10.0-19.0 years) was 14.8% (8/54) to 23.3% (27/116), which is strikingly higher than the 10% prevalence data reported for the general pediatric population.¹⁰ In fact, except for mentally retarded patients, pica is generally not seen in adolescence.¹⁰ This was a cross-sectional study of the prevalence of pica. It did not address the duration of pica. It is possible that the onset of pica among teenagers was in their early childhood and persisted for many years.

To better understand the cause for the high prevalence of pica among patients with SCD, the question of other possible causes of the more severe anemia needs to be explored. If iron deficiency or lead poisoning are not aggravating factors, perhaps other nutritional deficiencies should be explored. It has been proposed that zinc deficiency may be an occult cause of pica in many populations.^{2,3,6-8} Zinc deficiency in SCD has been well recognized.¹² The relationship between pica and zinc level was previously proposed with an anecdotal letter to the editor that described a child with pica for a common household cleanser that contains a substantial quantity of zinc (2 μ g/mg). The patient was subsequently given zinc supplementation, and a resolution of pica was seen

once serum zinc levels were restored to reference range.³ Zinc deficiency in SCD has been shown to be due to hyperzincuria from a decreased renal tubular reabsorption of zinc due to renal damage from repeated sickling.¹³ The effects of zinc deficiency include delayed growth, hypogonadism, problems with dark adaptation, and immune defects.¹⁴⁻¹⁷ One possible explanation is that zinc deficiency exists in most or all SCD patients, leading to a predisposition to development of pica. Pica behavior may actually be precipitated by additional factors, such as psychosocial stressors. A large number of patients with SCD face multiple socioeconomic challenges, as previously reported.⁹

Clearly, the etiology of pica in SCD remains elusive. This study demonstrates that pica has a significant prevalence rate among patients with SCD and merits further investigation. The roles of psychosocial factors in pica among children with SCD and the prevalence of zinc deficiency in this population need to be evaluated. The benefits of zinc therapy in resolving pica behavior should be considered.

Accepted for publication May 25, 2001.

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