ORIGINAL ARTICLES

Nutritional status, hospitalization and mortality among patients with sickle cell anemia in Tanzania

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ABSTRACT

Background

Reduced growth is common in children with sickle cell anemia, but few data exist on associations with long-term clinical course. Our objective was to determine the prevalence of malnutrition at enrolment into a hospital-based cohort and whether poor nutritional status predicted morbidity and mortality within an urban cohort of Tanzanian sickle cell anemia patients.

Design and Methods

Anthropometry was conducted at enrolment into the sickle cell anemia cohort (n=1,618; ages 0.5-48 years) and in controls who attended screening (siblings, walk-ins and referrals) but who were found not to have sickle cell anemia (n=717; ages 0.5-64 years). Prospective surveillance recorded hospitalization at Muhimbili National Hospital and mortality between March 2004 and September 2009.

Results

Sickle cell anemia was associated with stunting (OR=1.92, $P<0.001$, 36.2%) and wasting (OR=1.66, $P=0.002$, 18.4%). The greatest growth deficits were observed in adolescents and in boys. Independent of age and sex, lower hemoglobin concentration was associated with increased odds of malnutrition in sickle cell patients. Of the 1,041 sickle cell anemia patients with a body mass index z-score at enrolment, 92% were followed up until September 2009 (n=908) or death (n=50). Body mass index and weight-for-age z-score predicted hospitalization (hazard ratio [HZR]=0.90, $P=0.04$ and HZR=0.88, $P=0.02$) but height-for-age z-score did not (HZR=0.93, NS). The mortality rate of 2.5 per 100 person-years was not associated with any of the anthropometric measures.

Conclusions

In this non-birth-cohort of sickle cell anemia with significant associated undernutrition, wasting predicted an increased risk of hospital admission. Targeted nutritional interventions should prioritize treatment and prevention of wasting.

Key words: sickle cell anemia, nutrition, growth, anthropometry, Africa, mortality, morbidity.

Introduction

Sickle cell anemia (SCA) is one of the most common single gene disorders in the world, designated by the World Health Organization as a public health priority.[1] Knowledge of the natural history and improved management of SCA has been gained from systematic studies, largely in the USA and Jamaica. However, SCA is predominantly an African disease, with the majority of affected births (homozygous inheritance of hemoglobin S–[HbSS]) occurring in Africa.[2] Although SCA is a single gene disorder, the clinical expression and severity of the disease are surprisingly varied, and are thought to result from epistatic interactions from other genes and/or environmental factors.[3]

Energy and nutrient supplies are likely to be limited or compromised in SCA by a combination of factors: (i) reduced intake[4] potentially from the anorexic effects of co-morbidities;[5] (ii) decreased absorption of nutrients; (iii) increased degradation and losses of nutrients;[6] increased requirements from an elevated basal metabolic rate;[7] and alterations in metabolic pathways.[8,9] Poor growth has been previously documented in SCA.[10-12] However, the causes and clinical significance are not well understood.[13]

In Africa, where dietary intakes are sub-optimal for many populations, we hypothesized that nutrition is an important modifiable risk factor for SCA morbidity and that poor nutritional status is associated with increased mortality and morbidity. Here we describe anthropometric measures of nutritional status in a large cohort of Tanzanian SCA patients at enrolment. Factors associated with poor nutritional status and its consequences on mortality and morbidity are analyzed.

Design and Methods

Ethics statement

The study received ethical approval from Muhimbili University of Health and Allied Sciences reference MU/RP/AEC/VOL XI/33) and the London School of Hygiene and Tropical Medicine (reference 5158).

Patients and clinical procedures

Screening is not currently available for the newborn in Tanzania. Patients were recruited from the SCA clinic at Muhimbili National Hospital, the national referral hospital in Dar-es-Salaam, Tanzania, for five years from March 2004. Informed consent was obtained from patients or guardians at screening and at enrolment into the cohort. Anthropometric status of SCA patients at enrolment was compared to individuals screened for SCA but found to be either HbAA or HbAS during this recruitment period. All SCA patients are seen at scheduled routine visits (every 3-6 months) at the Muhimbili National Hospital SCA clinic and receive daily folate supplementation (5 mg/day) and anti-malarial prophylaxis according to Tanzanian government guidelines. Those subjects with SCA receive free public health care. Those with acute illness were referred from district health facilities or came directly to Muhimbili National Hospital emergency department and were managed or hospitalized according to hospital protocols.

Procedures at enrolment

Out of 1,982 screened patients with HbSS, 1,748 (88%) returned for enrolment and were issued with a unique identity number.

Physical examinations were performed and detailed histories were recorded, including history of dactlytis (painful inflammation of fingers or toes) and number of previous hospital admissions. Blood samples were collected for full blood counts (FBC), detection of malaria plus confirmation of HbSS status and fetal hemoglobin (HbF) fraction by high performance liquid chromatography (HPLC) and, for a period of time, a clinical chemistry panel were all carried out.

Procedures for detection of inpatient admissions to MNH, death and loss to follow up

SCA patients hospitalized at Muhimbili National Hospital were identified through daily ward surveillance. The decision to admit SCA patients was the responsibility of the attending clinician in the hospital casualty department, according to criteria of hospital protocols. SCA patients who did not attend scheduled clinic visits for 6-12 months or more were traced by telephone or home visits. SCA patients were followed up until September 2009.

Anthropometry

Height (nearest cm), weight (nearest 0.1 kg) were measured using standardized techniques. Z-scores for height-for-age (HAZ), weight-for-age (WAZ), and body-mass-index for age (BMIZ) were calculated for patients aged over 60 months against the UK1990 reference values using the zanthro programme[14] (STATA 9; StataCorp, College Station, TX, USA). For children aged under 60 months, WHO 2006/2007 reference values[15] were used using igrowup-stata (*http://www.who.int/childgrowth/en/*). Levels of malnutrition (stunting, underweight and wasting) were defined as Z-scores of less than -2 but more than -3 for moderate and less than -3 for severe. HAZ scores determined the severity of stunting, WAZ, underweight and BMIZ, wasting. Nutritional status centiles were plotted and internal z-scores for SCA generated using LMS chartmaker-Pro-v.2.3 (Tim Cole and Huiqi Pan. Copyright 1997-2006, Medical Research Council, UK).

Laboratory procedures

At screening or after an appropriate interval for patients who had recently had a blood transfusion, individuals were typed for HbS by alkaline Hb electrophoresis (Helena, Sunderland, Tyne and Wear, UK). At enrolment, hemoglobin fractions, including HbF, were quantified by HPLC using the β-thalassemia Short Programme on the Variant analyser (BioRad, Hercules, CA, USA) confirming the previous diagnosis. Full blood counts (FBC) were performed using an automated cell counter (Pentra 60, Horiba ABX, Kyoto, Japan). Biochemical tests were performed using an automated chemistry analyzer (Abbott Architect, NY, USA).

Statistical analysis

Data were analyzed using STATA ICv9. Internal *z*-scores were used to assess relative nutritional status within our SCA population (ensuring a normal distribution) with risk of mortality and risk of in-patient admission to Muhimbili National Hospital using Cox's regression with the Cnaan and Ryan approach, modeling the effect of age at enrolment.[16] Hospital admissions less than seven days apart were treated as a single event and the previous number of admissions was included as a co-factor when analyzing the risk of subsequent admissions. Adjustment for clustering within families (124 family groups [full or half siblings or mother/father child groupings]) was performed and repeated events within individuals accounted for using robust standard errors. The end date for observation was the date of last contact either at the clinic, through tracing activities or during a hospital admission, or date of death.

Table 1. Prevalence of malnutrition in SCA compared to non-SCA.

| | SCA | | Non-SCA | | |
	Mod n (%)	Sev n (%)	Mod n (%)	Sev n (%)	SCA *vs.* non-SCA* OR [95% CI]
Stunting HAZ-score	238 (23)	130 (13)	94 (17)	41 (7)	1.82 [1.43/2.32]
SCA (N=1024) non-SCA (N=562)					*P*<0.001
Underweight WAZ-score	240 (24)	115 (11)	84 (15)	44 (8)	2.61 [2.06/3.31]
SCA (N=1019) non-SCA (N=573)					*P*<0.001
Wasting BMIZ-score	105 (10)	55 (5)	59 (10)	18 (3)	1.66 [1.21/2.28]
SCA (N=1041) non-SCA (N=583)					*P*=0.002

*Mod: moderate (<-2 z-score>3 z-score); Sev = Severe (<-3 z-score). *Odds ratio of malnutrition (moderate and severe combined), adjusted for age (in years) and sex. Logistic regression models were limited to those with a valid BMIZ-score; clustering within families was adjusted by calculation of robust standard errors.*

Results

Height, weight, age, sex and a valid BMI were available for 1,041 SCA cases at enrolment (49% males) and for 717 controls (HbAS or HbAA). Cases were significantly younger than controls (mean 10.1 *vs.* 13.8 years, *P*<0.001). Overall, sex distribution was similar with 49% male cases *vs.* 48% in controls, but the proportion of males decreased significantly with age in both groups (*P*=0.001). Mean HbF% in SCA was 5.5 (SD=4.2; N=965 [>5y]) and mean hemoglobin 7.5g/dl (SD=1.4) *vs.* 11.0g/dl (SD=2.6) (*P*<0.001).

Nutritional status in Tanzanian SCA

Table 1 demonstrates a significantly increased prevalence of malnutrition (<-2 z-scores for HAZ, WAZ, and BMIZ) in SCA *versus* non-SCA. Centile plots displaying
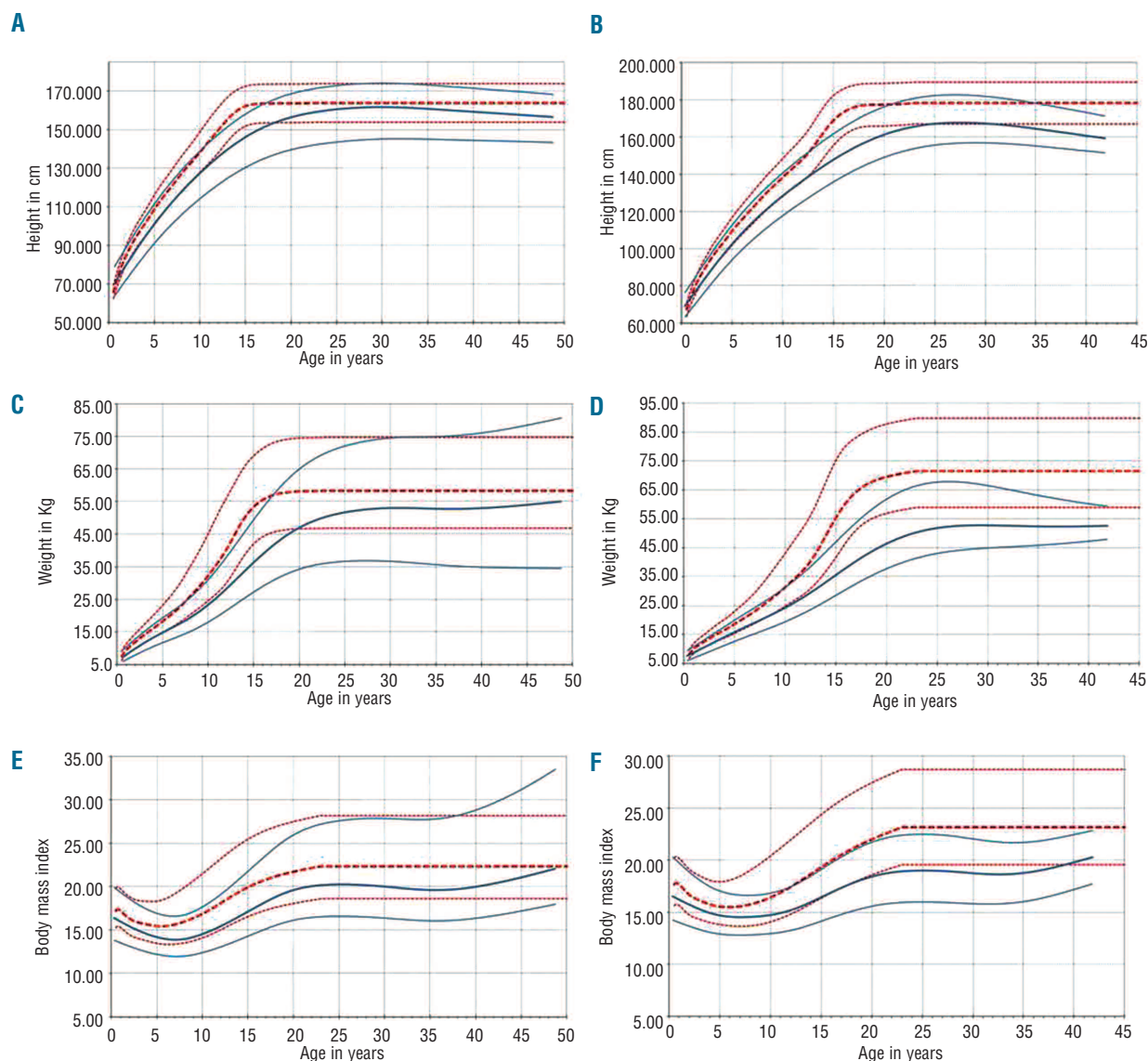
Figure 1. Height, weight and BMI centile plots for SCA compared to UK reference data.[14] (A, C) and (E) are for females and (B, D) and (F) for males. Red dotted lines are the 95th, median and 5th centile curves for UK reference data[14] (1990); solid blue lines represent the 95th, median and 5th centile curves for the Tanzanian SCA population. UK reference curves were extrapolated at the same level after the maximum age available of 23 years.

Table 2. Multivariable models of factors associated with malnutrition in SCA at enrolment into the cohort.

	Stunting (<-2 HAZ-score)		Underweight (<-2 WAZ-score)		Wasting (<-2 BMIZ-score)	
	OR [95% CI]	P value	OR [95% CI]	P value	OR [95% CI]	P value
Age in years	1.02 [1.00/1.04]	0.033	1.05 [1.03/1.07]	<0.001	1.06 [1.04/1.09]	<0.001
Hb [g/dL]	0.80 [0.72/0.89]	<0.001	0.86 [0.78/0.96]	0.005	0.96 [0.82/1.12]	0.62
Dactylitis in previous year	1.90 [1.31/2.76]	0.001	–	–	–	–
Unconjugated bilirubin	–	–	–	–	1.005 [1.0008/1.008]	0.017

Logistic regression models were limited to those with a valid BMIZ-score; clustering within families was adjusted for by calculation of robust standard errors. Age and sex were included in models a priori.

the 5th to 95th percentile ranges of height, weight and BMI in SCA at enrolment by age and sex compared to UK reference data are shown in Figure 1.

Stunting

The centile plots in Figure 1 demonstrate the greatest deficits in height in SCA during adolescence, but also an extended growth period and potential for catch-up growth, more pronounced for females (Figure 1), resulting in males being more likely to be stunted as adults (>18y, OR=2.48 [1.19/5.17] P=0.015).

Underweight

Adult males were seven times more likely to be underweight than females (OR=7.01 [3.21/15.50] P<0.001), whilst in the 5-10 years age group, males were less likely to be underweight (OR=0.52 [0.31/0.86] P=0.011). Figure 1 clearly demonstrates low weight in adolescence, most pronounced in males, and the large variation in weight for females.

Wasting

Wasting was most prevalent in adolescents and adults. However, the mean BMI in adults was 20.0 kg/m² (95% CI 19.5–20.5) and was thus considered to be within the healthy range (17.5-25 kg/m²). Similar to underweight status, adult males had an increased risk of wasting (OR=4.15 [1.95/8.82] P<0.001) but males aged 5-10 years had a significantly decreased risk (OR=0.50 [0.25/0.99] P=0.048).

Factors associated with increased odds of malnutrition at enrolment

When sex and age were included in multivariable models a priori, there was no effect of HbF%, generally reported to be a strong modulator of SCA disease severity, and associated with age and sex.[17] In multivariable models, the only significant variables were age, history of dactylitis, unconjugated bilirubin and Hb concentrations (Table 2).

Hemolysis, anemia and malnutrition in SCA

Unconjugated bilirubin and lactate dehydrogenase are considered markers of hemolysis and are reported to be associated with disease severity.[18] Raised levels of these markers were significantly associated with decreased hemoglobin concentrations (*data not shown*). However, none were significantly associated with nutritional status when age and sex (but not hemoglobin) were included in models, except for a positive association between unconjugated bilirubin concentrations and odds of wasting (P=0.037).

Table 3. Relative nutritional status within SCA and risk of hospital admission.

Univariable models	Events/N	Risk of hospitalization Hazard ratio [95% CI]	P value
HAiZ-score	415/975	0.91 [0.82/0.99]	0.048
WAiZ-score	415/975	0.87 [0.78/0.97]	0.009
BMIiZ-score	419/985	0.90 [0.82/0.99]	0.042
Hb [g/dL]	393/879	0.93 [0.87/0.99]	0.037
Multivariable model stunting			
HAiZ-score	393/879	0.93 [0.84/1.03]	0.16
Hb [g/dL]		0.95 [0.88/1.01]	0.094
Multivariable model underweight			
WAiZ-score	389/869	0.88 [0.79/0.98]	0.017
Hb [g/dL]		0.95 [0.98/1.02]	0.14
Multivariable model wasting			
BMIiZ-score	393/879	0.90 [0.82/0.99]	0.043
Hb [g/dL]		0.94 [0.88/0.99]	0.046

Cox's regression models are controlled for age at enrolment, sex and previous number of hospital admissions.

Nutritional status at enrolment and risk of mortality

Internal z-scores were used to assess how relative nutritional status of individuals was associated with mortality. Of the 1,041 SCA patients with a BMI z-score at enrolment, 958 (92%) were followed up until September 2009 or until death (n=50). Median follow up was 2.1 (range 0.02-5.4) years. The incidence rate of death was 2.5 per 100 person years observation (PYO) (95% CI 1.9-3.3), similar to the full cohort at 2.0 per 100 PYO.[19] Controlling for age at enrolment, and stratified by age group, there was no evidence of an association between nutritional status at enrolment and risk of mortality, for example: BMI-internal z-score (BMIiZ score) hazard ratio [HZR]=1.02 [95% CI 0.76-1.37; P=0.91] and no difference according to sex. However, as for the whole cohort,[19] hemoglobin concentrations were significantly negatively associated with mortality, with a 30% decrease in risk per g/dl increase in hemoglobin (HZR=0.69, [95% CI 0.56-0.85], P=0.001) when limited to this population with anthropometric data.

Nutritional status at enrolment and risk of hospitalization

Of the 1,041 with BMIZ scores at enrolment, 985 returned for at least one routine follow-up visit and were included in this analysis. There were 419 admissions in 385 (36%) subjects; 238 of these contributing one event only (maximum number of events per person was 11) and a total of 2,378 PYO. There were 17.6 (95% CI 16.0-19.4)

admissions per 100 PYO. Independent of age at enrolment, poorer nutritional status was significantly associated with increased risk of hospitalization (Table 3), with the greatest effect size for relative weight-for-age (greater WAiZ score, HZR=0.87, *P*=0.009), equivalent to a 13% reduction in risk for each increase in WAiZ score of one SD. Baseline hemoglobin concentration was also negatively associated (HZR=0.93 per 0.1g/dl, *P*=0.037). Baseline hemoglobin and BMIiZ score were independently associated with risk of admission (Table 3). Sex had no effect on hospitalization (HZR=0.95, *P*=0.50).

Discussion

Prevalence of malnutrition in SCA by age and sex

This is one of the largest analyses of nutritional status of SCA patients at a single site, and certainly within Africa. Our data suggest a similar or lower prevalence of malnutrition in SCA compared to other African studies.[20-22] Unsurprisingly, compared to patients enrolled in comprehensive care programs in the USA[23,24] or the UK,[25] Tanzanian SCA patients experience a greater prevalence of malnutrition compared to local controls. For example, in 178 American SCA children (0-18 years), the proportion who were ever less than the US National Center Health Statistics (NCHS) 5th percentile for height, weight or BMI during four years of follow up was 22-26%,[12] compared to 36-38% less than the 2.5th percentile (<-2 SD) for height and weight in our cohort at baseline. However, only 18% of our cohort were less than the 2.5th percentile for BMI, suggesting adaptation to chronic energy/nutrient deficiency, perhaps from slowed rates of growth and stunting. Alternatively, it may represent a survivor cohort effect.

Differences in nutritional status according to sex within SCA have been reported previously. In most cases, similar to our study, nutritional status was worse in males compared to females[11,26-28] although one study reported the contrary.[29] However, in the one study that assessed disease severity in relation to growth, effect was limited to females.[12] Disparity between the age groups in these studies and differences in effects of SCA on pubertal delay between males and females may underlie these discrepancies. We observed that the most growth retardation was experienced in adolescents. This is likely, at least in part, an artifact from delayed and extended puberty, particularly in females which allows for a substantial degree of catch-up growth. This has already been seen in Jamaican patients, for whom longitudinal centile growth curves were plotted and reference data generated.[11] The reasons why females should experience more catch-up growth than males is not clear.

Clinical impact of nutritional status in SCA

We believe that this is the first report that has attempted to assess the relationship between nutritional status and mortality within SCA. In the UK East London Cohort with a very high rate of survival,[25] malnutrition is uncommon with only 6.5% of 2-15 year olds having a *z*-score of less than -2 for weight-for-age and 4.2% for height-for-age or BMI[13] suggesting that improved nutritional status may have increased survival or that increased care has resulted in milder disease and improved nutritional status. Supporting the latter possibility, hydroxyurea therapy has been associated with a

decrease in resting energy expenditure, correlated with increased HbF expression, and decreased wasting.[5] The lack of an association between nutritional status and mortality in our cohort is, therefore, surprising. There is strong evidence to show that poor nutritional status is a contributory factor for mortality in children in general.[30-32] Furthermore, we observed strong associations between hemoglobin and nutritional status and between hemoglobin and mortality; in addition poor nutritional status at enrolment was associated with risk of hospitalization, expected to be a good indicator of disease severity. It is possible that an effect of malnutrition on mortality in our SCA population is limited to young children who have the highest mortality among SCA patients, due particularly to infections,[25,33-35] including in our cohort.[19] Malnutrition may have the greatest effect on mortality when mediated through an interaction with infections, as suggested in a Kenyan study in which the majority of deaths in young children attributable to malnutrition were ascribed to infection as the immediate cause of death.[36] In the absence of newborn screening, this *survivor* cohort, with a small number of patients in the youngest, most vulnerable age group, may have resulted in a lack of power to detect a true association. Reduced growth may also be an adaptation to a chronic undersupply of energy and nutrients, reducing total energy requirements, and allowing available energy and nutrients to be directed towards maintaining essential metabolic defenses against disease processes. Smaller body size will also ameliorate the effects of chronic anemia on cardiac load. The lower prevalence of wasting compared to stunting and underweight may support this hypothesis. Good nutritional status was not found to predict a benign clinical course in Jamaican SCA patients, also indicating an element of protective adaptation.[37] Finally, although wasting and underweight were risk factors for hospitalization, stunting was not. Therefore, wasting may represent a failure of the adaptive processes or alternatively be precipitated by events that lead to the hospital admission. Unfortunately, the cause of death remains unknown for the majority of cases in our cohort, due to the high number of deaths that occurred in the home.[19]

Conclusions

In our urban setting, sickle cell anemia is associated with a high prevalence of malnutrition and growth retardation in patients of all ages, but particularly in adolescents. Contrary to expectations, there was no evidence of an association between malnutrition and mortality during the 5.5 year period of follow up, although there was an association with symptomatic disease as captured by data regarding hospitalization. A birth cohort and analysis of growth rates with hospitalization and other indicators of disease severity in different age groups is required to determine relationships between malnutrition and SCA disease outcome.

The relationships between hemoglobin concentration, nutritional status and severity of disease, and the potential effects and extent of delayed pubertal development warrant further longitudinal investigation. Nutritional interventions may play an important role in enhancing healthy survival rates in SCA patients, but need to be appropriately tested before widespread implementation can be recommended.

Authorship and Disclosures

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