Research Article

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Prevalence of Hematological Abnormalities and Factors Associated Among HIV-Infected Children Receiving Care at Kilimanjaro Christian Medical Centre

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Abstract

Background

In HIV infected children, any of the cell lineages can be depressed during disease progression. Hematological complications such as anemia, neutropenia and thrombocytopenia were among clinical problem frequently reported in early years of AIDS. This study aimed to determine the magnitude of hematological abnormalities and factors associated with HIV infected children.

Methods

A cross-sectional analytical hospital based study was done from Sept 2016 to May 2017, and 201 HIV-infected children, below 14 years attending ART clinic during the study period were included. Social and nutrition history, ARV drugs used, clinical staging and anthropometric measurements were recorded. Blood samples for full blood count and HIV viral load were taken and analyzed by Mindray BC 5380 and Roche COBAS respectively. Data analysis was done using STATA where descriptive statistics for categorical variables were summarized using frequency and percentage. Odds Ratio (OR) with its 95% CI was used to measure the association between dependent variables and independent variables by using logistic regression.

Results

The median age of the participants was 9 years. Most of them 44.78% were on zidovudine, lamivudine and Nivirapine regimen combination therapy. Prevalence of anemia, neutropenia and thrombocytopenia was found to be 42 (20.9%), 41 (20.4%), 4 (2%), respectively. Children under five years (OR 2.36, 95 % CI, 1.06-5.27) had higher viral load >1,000 copies /mil, (OR 2.02, 95% CI, 1.01-4.07), those taking co-trimoxazole (OR 2.67, 95% CI, 1.31-5.46), those who had history of TB disease (OR 2.09, 95% CI, 0.92-4.75), and those with less than one year on ART (OR 3.14, 95 % CI, 1.02-9.63) were associated with anemia in bivariate analysis. However, in multivariate analysis for anemia, no factor remained significant. Having history of TB had higher odds of developing neutropenia (OR 2.18, 95% CI, 0.96-4.95) although it was not significant.

Conclusion

The prevalence of anemia and neutropenia in children is still high despite being on ARVs. Under-fives, taking co-trimoxazole, having higher viral load, TB disease history and being on ART for less than one year were are risks of developing anemia. Regular monitoring of hematological abnormality may help identify problems early and appropriate measures taken to prevent the effect of these abnormalities.

Keywords: Anemia, Thrombocytopenia, Neutropenia, HIV Tanzania

Introduction

Hematological abnormalities have been documented to be a second most common cause of mortality and morbidity in HIV patients [1]. Globally, there were 36.7 million adults and children estimated to be living with HIV by 2015 and 1.1 million people were estimated to have died due to AIDS related causes worldwide (UNAIDS, 2016) [2]. It is estimated that in 2013, 240,000 children younger than 15 years of age were newly infected with HIV bringing the total number of children living with HIV worldwide to 3.2 million or approximately 9 percent of all people living with HIV [3].

Hematological abnormalities such as anemia, neutropenia and thrombocytopenia in children infected with HIV, were among clinical problems frequently reported in early years of acquired immune deficiency syndrome [4]. The origin of hematological abnormalities remains incompletely understood but may be due to myelosuppression caused by HIV attributable dysfunctional hematopoiesis and contribute to morbidity and mortality [5,6].

Anemia is the most frequent hematological abnormality found in patients living with HIV, even in patients who are on antiretroviral therapy, it has been associated with impairment of quality of life [4]. Most common type of anemia in HIV-infected patients is normocytic normochromic [7]. The magnitude of anemia varies and it is estimated that up to 90% of HIV patient's adults and children develop anemia during their infection period [4]. The prevalence of anemia in children with HIV depends on several factor such as stage of HIV infection, sex, age, race, concurrent illness and nutritional status [8].

Neutropenia is present in up to 70% of HIV- infected patients and it is reported to be more common with advanced stage of disease, especially patients with low CD4 count and at WHO stage four, while thrombocytopenia present in up to 40% of infected HIV patients and it can occur at any stage of disease [9,10,11].

Hence the aim of this study was to determine the prevalence of hematological abnormalities and factors associated among HIV children receiving care at Kilimanjaro Christian Medical Centre.

Methodology

Study Design, population and Site

This cross-sectional analytical hospital based was conducted from September 2016 to May 2017 involving children attending for care and treatment at Child Centered Family Care Clinic (CCFCC) at Kilimanjaro Christian Medical Centre (KCMC). The CCFCC was established early 2007. It provides care for children infected with their families while maintaining a focus on care, training and research. The CCFCC has cooperation between KCMC, Duke University and Elizabeth Glacier Pediatric Association Foundation. The children seen in the clinic are from different places from Kilimanjaro region and some from Arusha region. At a time of study, clinic had a total of 435 registered HIV-infected children including adolescents on regular follow-up. All children aged less than 14 years who were confirmed HIV-positive and were on ART and their parents or guardian consent were included. All HIV children documented to have diseases like Sickle cell disease, or receiving chemotherapy and whose parents or guardian refuse to sign consent were excluded.

Sampling Technique

All children aged less than 14 years who were confirmed HIV positive and had been on ARVS's who met the inclusion criteria during the study period were enrolled in the study until sample size of 208 was archived.

Study Procedure

Following attainment of informed written consent, the principal investigator followed a questionnaire-guided interview to obtain demographic data and physical examination was conducted.

Data Collection Tool and Methods

A standardized questionnaire was used to record the information obtained from every patient including laboratory data from full blood picture and viral load result. Social demographic characteristics, nutrition history, ARV drugs used, clinical staging, physical findings and anthropometric measurements were recorded. Bodyweight in kilograms and height (in meters, to the nearest cm) was measured. Height was measured using a steadiometer while those who were not able to stand length was taken by using non-stretchable seca. Mid-upper-arm circumferences were taken, where the arm length was measured from the olecranon process to the acromion process and half way between these two points the circumference was measured by using a non-stretchable MUAC tape which comes in different types according to the age group. Thereafter 6mls blood was collected for viral load and FBP. Sample for FBP includes WBC, neutrophil, lymphocytes and their differentials, hemoglobin, platelets and all red blood cell indices erythrocyte, hematocrit, min cell volume, min cell hemoglobin. Patient's specific study identification number was used.

The blood samples were carried out to KCMC laboratory by using biohazard bag with the study laboratory request forms for analysis. Thereafter, Full blood picture samples were taken to hematology section, and viral load samples were taken to molecular section for analysis. Anemia and neutropenia were defining according to Tanzania guideline for HIV, below normal level of hemoglobin (Hg) according to age <2 years' hemoglobin <10 g/dl, and for >2years hemoglobin <11g/dl. Neutropenia was defined as absolute neutrophil count <1.2x10^9/l. While thrombocytopenia was defined as platelets counts 100x109/l [12].

Laboratory Analysis

Full blood picture was analyzed by Mindray BC-5380 Auto-hematology Analyzer, Manufacturer at Shenzhen Mindray Bio Medical Electronics Co. Ltd. Germany: 2008. While viral load was analyzed by Roche COBAS Ampliprep/Cobas Taqman 48 manufacturer-ROCHE; Sensitivity 100%, Specificity 100%; Place: Switzerland year 2009. All samples were analyzed within 24 hours after collection.

Data Analysis

Data were checked for completeness and entered into Statistical Package for Social Science version 20 (SPSS Version. 20) and analyzed using STATA version 13. Descriptive statistics for categorical variables were summarized using frequency and percentage. Odds Ratio (OR) with its 95% CI was used to measure the association between dependent variables and independent variables by using logistic regression. In multivariate analysis

all covariates with p <0.10 in the univariate analysis was added to the multivariable model. P value of less than 0.10 with 95% confidence interval was used to estimate statistical significance of the association. Nutritional status of the children was analyzed using WHO anthro and anthroplus software 2007 and was expressed as standard deviation and categorized. Those who were having less than or equal -2 SD was categorized into grade 1 to 3 thinner (underweight). Those who were >-2 SD to + 2SD were categorized as normal weight and those > = +2 SD were categorize as overweight.

Results

During study period a total of 208 children on ART were recruited in the study and blood samples for FBP and viral load collected from each one. Two blood samples for FBP clotted and five participants missed required information; therefore, results for 201 HIV participants were analyzed.

Characteristics of HIV children who attending CCFCC clinic at KCMC

A total of 201 HIV infected children were analyzed. The mean (SD) age of study participants was 9 (±3.51) years, with most of them 166 (82.6%) being in the age group above 5 years. There was slightly high proportion of female 111 (55.5%) as compare to male participants 89 (44.5%). Almost half, 108 (53.73) of the study participants came from urban area whereas, 93 (46.27%) were residing in the rural. Majority 131 (65.17%) of study participants' caretakers had attained primary education, whereas, 11 (5.47%) had not attained any education. Majority 192 (95.52%), were living with their caretaker/parents whereas, 9 (4.48%) were living in orphanages.

Table 1: Socio-demographic characteristics of HIV infected children receiving care at CCFCC-KCMC Hospital (N=201)

Characteristics	n (%)
Mean (SD) age	9.31 (3.51)
Age group	
<5 years	35 (17.4)
≥5 years	166 (82.59)
Gender	
Female	112 (55.5)
Male	89 (44.5)
Place of residence	
Rural	93 (46.27)
Urban	108 (53.73)
Education of caretaker	
Primary	131 (65.17)
Secondary	44 (21.89)
Tertiary	15 (7.46)
Unknown	11(5.47)
Living in Orphanage	
No	192(95.52)
Yes	9(4.48)

Prevalence of Anemia, Neutropenia and Thrombocytopenia

Majority, 159 (79.10%) had normal hemoglobin level and 42 (20.9%) participants with below normal hemoglobin (Figure 1), where majority 27 (64.3%) had grade one severity. Majority of the patients had normal neutrophils level 160 (79.60%) whereas, 41 (20.40%) had neutrophils level below normal (Figure 2). Most of the participant had normal level of platelets 197 (98%) whereas, only 4 (2%) had lower than normal level of platelets (Figure 3). Therefore, overall prevalence of Anemia was 20.9%, Neutropenia 20.4% and Thrombocytopenia 2%.

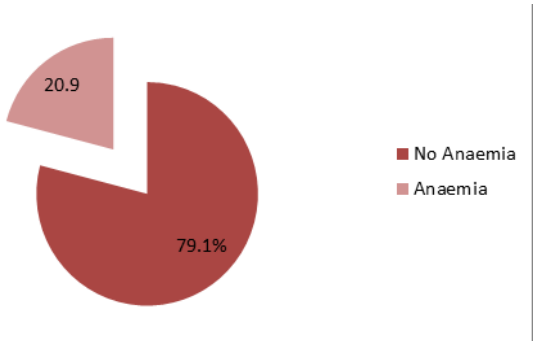

Figure 1: Prevalence of anemia among HIV children attending CCFCC clinic at KCM

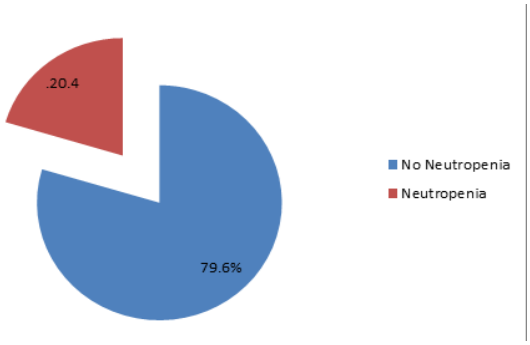

Figure 2: Prevalence of neutropenia among HIV-infected children patients attending CCFCC clinic at KCMC

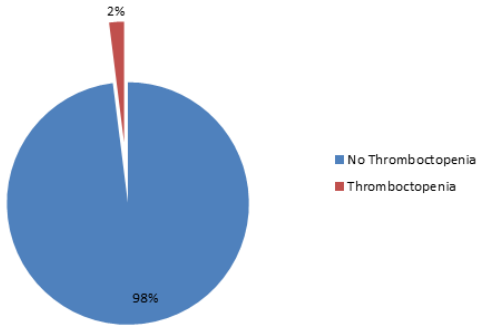

Figure 3: Shows the prevalence of thrombocytopenia among HIV-infected children attending CCFCC clinic at KCMC hospital during the study period

Factors Associated with Anemia in HIV Children Attending CCFCC Clinic at KCMC

In crude analysis age below five years had higher risk of developing

anemia compared to those above five years (OR: 2.36, 95% CI, 1.06-5.27), Being on co-trimoxazole increased odds of developing anemia as compared to those whom co-trimoxazole had been stopped (OR: 2.67, 95% CI, 1.31-5.46). Participants who had viral load above 1000 copies/ml had two times higher chances of developing anemia as compared to those who were having viral load below 1000 copies/ml (OR: 2.02, 95% CI, 1.01-4.07). Those children on ART for less than a year had more than three times higher chances of developing anemia as compared to those who were on treatment for more than a year (OR: 3.14, 95% CI 1.02-9.63). No any ART drug which showed statistical significant association with anemia. However, there were slightly increased odds of developing anemia for EFV, ABC and LPV/R by 12%, 71% and 77%, respectively with slightly reduced odd of developing anemia for AZT and NVP by 28% and 44%, respectively.

In multivariate after controlling for other factors, age, having history of Tb, higher viral load above 1,000 and duration of ART less than one year remains with higher odds of developing anemia although it was not statistically significant.

Table 2: Factors associated with anemia

Characteristics	No Anemia	Yes anemia	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age group						
≥5	136 (81.9)	30 (18.0)	1		1	
5	23 (65.7)	12 (34.2)	2.36 (1.06-5.27)	0.035	1.28 (0.493.34)	0.606
Gender						
Male	72(80.90)	17 (19.1)	1			
Female	87(77.68)	25 (22.3)	1.21 (0.60-2.42)	0.577		
WHO clinical staging						
1	13 (72.2)	5 (27.7)	1			
2	42 (87.5)	6 (12.5)	0.37 (0.09-1.41)	0.147		
3	60 (80.0)	15 (20.0)	0.65 (0.20-2.10)	0.473		
4	44 (73.3)	16 (26.6)	0.94 (0.29-3.07)	0.926		
History of TB						
No	136 (81.4)	31 (18.5)	1			
Yes	23 (67.6)	11 (32.3)	2.09 (0.92-4.75)	0.076	1.83 (0.77-4.34)	0.779
Taking co-tri-moxazole						
No	91 (86.6)	14 (13.3)	1		1	
Yes	68 (70.83)	28 (29.1)	2.67 (1.31-5.46)	0.007	1.89 (0.83- 4.27)	0.124
BMI for age						
Normal	83 (79.8)	21 (20.1)	1			
Underweight	67 (79.7)	17 (20.2)	1.00 (0.49-2.05)	0.994		
Overweight	9 (69.2)	4 (30.7)	1.75 (0.49-6.26)	0.385		
Viral load						
<1000	113 (83.0)	23 (16.9)	1		1	
>1000	46 (70.7)	19 (29.2)	2.02 (1.01-4.07)	0.047	1.61 (0.77-3.40)	0.204
Use of anti-hel-minthics						
Yes	70 (81.4)	16 (18.6)	1			
No	89 (77.3)	26 (22.6)	1.27(0.63-2.56)	0.490		
Current ARVs						
AZT: (No)	54 (73.9)	19 (26.0)	1			

(Yes)	105 (82.0)	23 (17.9)	0.62 (0.31-1.24)	0.179		
EFV: (No)	121 (79.6)	31 (20.3)	1			
(Yes)	38 (77.5)	11(22.4)	1.12 (0.51-2.46)	0.758		
ABC: (No)	104 (82.5)	22 (17.4)	1			
(Yes)	55 (73.3)	20 (26.6)	1.71 (0.86-3.42)	0.123		
LPV/r: (No)	115 (82.1)	25 (17.8)	1			
(Yes)	44 (72.1)	17 (27.8)	1.77 (0.87-3.60)	0.111		
NVP: (No)	83 (74.7)	28 (25.2)	1			
(Yes)	76 (84.4)	14 (15.5)	0.54 (0.26-1.11)	0.096	0.62 (0.29-1.33)	0.225
Duration on ART						
>1 year	8(57.14)	6(42.86)	1			
<1 year	151(80.75)	36(19.25)	3.14 (1.02-9.63)	0.045	1.81(0.51-6.36)	0.350

Association between Neutropenia and characteristics of HIV patients attending CCFCC clinic at KCMC

In crude analysis, factors like history of TB where (OR: 2.18, 95% CI, 0.96-4.95), higher viral loads above 1000 (OR: 1.65 95% CI, 0.81-.3.35), patients on AZT (OR: 1.48, 95% CI, 0.70-3.13), and NVP (OR: 1.56, 95%CI 0.78-3.12) had higher odds of developing neutropenia. For abacavir and LPV/r regime had less risks of developing neutropenia (OR: 0.63, 95% CI, 0.30-1.34) and (OR: 0.48, 95% CI 0.21-1.13) respectively. In adjusted analysis having TB disease history remained with higher odds (OR: 2.09, 95% CI, 0.91- 4.79) of developing neutropenia. Those who were on LPV/r drug had less risk of developing neutropenia compared to the counterparts.

Table 3: Factors associated with Neutropenia

Characteristics	No neutropenia n=160 (79.6%)	Yes neutropenia n=41 (20.4%)	Crude OR (95% CI)	p- value	Adjusted OR (95% CI)
Age group					
≥5	26 (74.2)	9 (25.71)	1		
<5	134 (80.7)	32 (19.28)	0.68 (0.29-1.61)	0.392	
WHO clinical staging					
1	13 (72.2)	5 (27.7)	1		
2	38 (79.1)	10 (20.8)	0.68 (0.19-2.3)	0.550	
3	62 (82.6)	13 (17.3)	0.54 (0.16-1.7)	0.319	
4	47 (78.3)	13 (21.6)	0.71 (0.21-2.3)	0.590	
History of TB					
No	137 (82.0)	30 (17.9)	1		1
Yes	23 (67.6)	11 (32.3)	2.18(0.96-4.95)	0.062	2.09(0.91- 4.79)
Taking co-trimox-azole					
No	84 (80.0)	21 (20.0)	1		
Yes	76 (79.1)	20 (80.8)	1.05 (0.52-2.09)	0.884	
Viral load					
<1000	112 (82.3)	24 (17.6)	1		
>1000	48 (73.8)	17 (26.1)	1.65 (0.81-3.35)	0.164	
Current ARVs					
AZT: (No)	61 (83.5)	12 (16.4)	1		
(Yes)	99 (77.3)	29 (22.6)	1.48 (0.70-3.13)	0.295	
EFV: (No)	122 (80.2)	30 (19.7)	1		
(Yes)	38 (77.5)	11 (22.4)	1.17 (0.53-2.57)	0.682	
ABC: (No)	97 (76.9)	29 (23.0)	1		
(Yes)	63 (84.0)	12 (16.0)	0.63 (0.30-1.34)	0.235	
LPV/r: (No)	107 (76.4)	33 (23.5)	1		
(Yes)	53 (86.8)	8 (13.1)	0.48 (0.21-1.13)	0.095	0.50 (0.21-1.18)
NVP: (No)	92 (82.8)	19 (17.1)	1		
(Yes)	68 (75.56)	22 (24.4)	1.56 (0.78-3.12)	0.202	
Duration on ART					
>1 year	149 (79.68)	38 (20.3)	1		
<1 years	11 (78.57)	3 (21.4)	1.06 (0.28-4.02)	0.921	

We couldn't do factor associated with thrombocytopenia due to low prevalence of thrombocytopenia.

Discussion

Hematological abnormalities in HIV infected children such as anemia have been shown to predict disease progression and mortality although the mechanism and causative role of HIV altering bone marrow thus inhibit hematopoiesis is uncertain. In Tanzania there is a lack of data related to HIV hematological abnormalities. The finding of this study however partially fill the gap. Among

the children participated in this study the overall prevalence of anemia was found to be 20.9% which is consistence with other studies done in east Africa which report ranges from 15% to 93% [8]. It is nearly similar prevalence which was reported in Ethiopia 21.9%, 22.2% Addis ababa, Our study show low prevalence compared to the another study done in India 69%, Lagos Nigeria 77.9 [13,14]. Muhimbili Tanzania report the prevalence of 44% [15]. This difference could be attributed to the definition of anemia they use, which was high Hg<11g/dl which could possibly increase the prevalence, age and small sample size. But also our study shows high prevalence compared to other studies. One study done in Nigeria which report prevalence of anemia of 3%. But this could be due to age and definition of anemia they use definition of anemia Hg <8g/dl. According to grading of hematology toxicity or anemia severity our study found that most of the participant who had anemia fall into grade 1 (64.2%), which is also consistence to the study reported by Muluneh in Ethiopia they also found that majority of the children fallen at grade1 severity (64.3%).

In our study the common type of anemia was normocytic normochromic. In our study it was least expected that those who are on AZT will have less risk to have anemia, this could be attributed to the fact that those who are on AZT were older children, as we have seen early that above five years are lower risk this could probably counter effect. This finding was also consistence with the finding in HIV adult women reported in New York they found that there were no association between anemia and being on AZT 0R 1.03(0.87-1.22) [7,16]

In our study Neutropenia was seen with the prevalence of 20.4%, this was high compared to prevalence of neutropenia which was reported in Jimma Ethiopia which was 4.7% this difference could be attributed due to different definition of neutropenia they used absolute neutrophil count of < 1000/mm3. But also our find is low compared to another study reported by Enawgaw and colleagues at Gondar Ethiopia they found the prevalence of neutropenia 35.4% [10]. This difference could be due to different cutoff value of neutrophilia they used. The former use neutrophils level <100 while at Gondar they use Neutrophils level below 150. The explanation for higher prevalence is HIV direct infect the bone marrow and stromal cell which may reduce hematopoiesis

Prevalence of Thrombocytopenia was found to be 4(2%) which also consistence with other studies in Nigeria they report the prevalence of 2.5% [14]. While in Ethiopia found prevalence of thrombocytopenia 7.8% Muluneh et al. 2011. Our finding is low compared to the thesis done in Uganda the prevalence was 24%, Munyagwa et al. 2007 (unpublished work) and Ethiopia 25 (8.3%) [17,18]. This difference could be attributed due to cutoff value for thrombocytopenia which they use which was < 150,000 which could possibly increase the prevalence also the duration of ART which was shorter to the previous study shorter. Longer duration of ART protects from getting hematological abnormalities because it suppresses the viral load these could possible decrease the effect of HIV to hemopoietin stem cell. In our study most of the participant had longer duration on ART. In our study among all 4 children who had thrombocytopenia 2 patient presented with the complication of thrombocytopenia, they had history of recurrent epistaxis.

On factor associated with Anemia our study found that factor like age, higher viral load, history of previous TB was significant associated with anemia but after controlling of confounder it was not statistical significant. Patients who are on AZT regime was shown to have less risk of having anemia this could be attributed to the effect of drug combination which could decrease risk of AZT associated anemia. Our finding was different from one study done in Uganda by Ruhinda and colleagues they found that taking cotrimoxazole prophylaxis was significant associated with anemia [19]. In our study it was least expected that those who are on AZT will have less risk to have anemia, this could be attributed to the fact that those who are on AZT were older children, as we have seen early that above five years are lower risk this could probably counter effect. But also from the current review reported by Volberding they report that use of zidovudine in HAART is not significant associated with anemia [20]. This finding was also consistence with the finding in HIV adult women reported in New York and Brazil they found that there were no association between anemia and being on AZT 0R 1.03(0.87-1.22) [7,16]

Our study didn't find any factor associated with neutropenia compared to Abebe and colleagues they find that all patient who had neutropenia were on AZT [21].

Conclusion

In this study we have seen the prevalence of anemia and neutropenia was high and nearly similar. However, thrombocytopenia was low. Age below five years, taking co-trimoxazole, higher viral load above 1000, having history of TB disease had increased odd of having anemia whereas history of TB disease, use of AZT or NVP had higher odd of neutropenia with lower odds for LPV/r regimen. Regular monitoring of hematological parameters for people leaving with HIV is importation on understanding the effect in long term ARVs use and time for prophylactic intervention and decision to change ARVs in case of severe anemia or neutropenia.

Limitation

In this study CD4 count was not done due to the none availability of reagent at the time the study was started. Bone marrow aspiration was note done.

Other limitation it is a cross sectional study which make association of hematological abnormalities being difficult. Also we couldn't do other modifiable such as intestinal parasite, infection with malaria, viral and fungal infection which could potentially contribute to high magnitude of hematological abnormalities. We didn't include non HIV patient as a control to compare the magnitude.

Recommendation

Large study multicenter prospective studies need to be conducted to explore modifiable associated factors of these hematological abnormalities,

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