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Research Article

Prevalence and Factors Associated with Tb/HIV Co-Infection among Severely Acute Malnourished Children Admitted in Mulago National Referral Hospital

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Abstract

Objectives: To determine the prevalence of Tuberculosis (TB)/Human Immunodeficiency virus (HIV) co-infection among severely malnourished children admitted in Mulago National Referral Hospital and determine the factors associated with co-infection in these children.

Methods: This was a cross sectional study design which consecutively enrolled children aged 1 - 5 years who were severely malnourished, consented to the study and were admitted during the study period. We excluded children with severe co-morbidities which would otherwise increase risk of TB. A standardized questionnaire, HIV serology, MTB RIF gene x-pert on gastric aspirates, a tuberculin skin test (TST), MUAC, weight for Height Z scores and chest x-ray were performed on all children. HIV positive children who fulfilled criteria for TB diagnosis clinically or microbiologically were considered to have TB/HIV co-infection.

Results: A prevalence of TB/HIV co-infection of 20.2% (35/173) was found. Associated factors included positive contact of PTB AOR 10.7, (95% CI: 3.9 - 34.9), missed Bacilli Calmette-Guerin (BCG) vaccine AOR 1.2, (95% CI: 0.72 - 0.6), hypothermia AOR 10.7, (95% CI: 1.5 - 51.6), lymphadenopathy AOR 11.3, (95% CI: 2.1 - 39) and hepatomegaly AOR 6.2 (95% CI: 1.5 - 14.5).

Conclusion: While there was a high prevalence of TB/HIV co-infection, missed opportunity for early ART and IPT initiation was very high. Strengthening of implementation of guidelines on screening and initiation of TB, HIV treatment should be emphasized. High index of suspicion for all malnourished children presenting with hypothermia, lymphadenopathy and hepatomegaly.

Keywords: *TB/HIV co-infection; SAM-NE; SAM-E; PTB; HIV*

Introduction

Tuberculosis (TB) and Human Immunodeficiency Syndrome (HIV) remain among the leading causes of death in children in the world today with severe malnutrition being indicated as a consequence for both [1,6].

The high mortality of children seen in South and East Africa has been attributed to presence of TB/HIV co-infection [5]. TB/HIV rate has been steadily increasing despite several initiatives to eliminate and reduce burden of TB/HIV with Africa recording the highest burden at 30% [1,8].

This study aimed to contribute to closing of this gap by determining the prevalence of TB/HIV co-infection among severely malnourished children and further documenting associated factors. At a national level the study aimed to inform strategy on increasing utilization of HAART, Cotrimoxazole (CTX) and TB screening for all malnourished children and thus ultimately improve the outcome of all severely malnourished children. The identified associated factors for TB/HIV co infection will be used to facilitate rapid identification of children at risk by health workers and therefore contribute to the timely diagnosis and management which will impact on reduction of the mortality and morbidity in this interest group. At a global level results can be generalized to countries that have a high TB/HIV burden through providing evidence-based information in terms of associations and diagnosis of TB/HIV in severe malnutrition.

Methods

Sample size

Using a sample size formula by Kish-Leslie for cross sectional studies:

$$N = \frac{Z\sigma^2 P(1-P)}{\delta^2}$$

Where N= sample size estimate of severely malnourished children with TB/HIV co-infection.

P= assumed true population prevalence of children with HIV/TB infection among severely malnourished children using a prevalence of 34% HIV infection rate in this group of severely malnourished children.1-P is the probability of not having TB/HIV thus 1-P=66%Z is the standard normal deviation at 95% confidence level corresponding to 1.96= absolute error between estimated and true population prevalence of TB/HIV co-infection of 5% Sample size = 1.96*1.96(0.26*0.66)/0.05*0.05 = 0.4056/0.0025 = 169. Calculation for associated factors was also performed using the kish-leslie and the larger sample size of 169 was used.

Study setting

The study was a cross sectional design and participants were recruited progressively at Mulago National Referral Hospital by well-trained research assistants or the principle investigator. The main recruitment site for this study was acute care unit which is the start point for all sick children receiving an average of 60 - 80 patients daily who are admitted in this unit and later transferred to the admission wards according to their diagnosis. Other children admitted in the nutrition ward who would have been missed in the Acute care unit were also recruited. Mulago Hospital sees children referred from all parts of Uganda and from neighbouring countries including Rwanda, DRC, South Sudan and Burundi.

Inclusion and exclusion criteria

All children aged between 1-5 years that were HIV positive and were severely malnourished as per WHO diagnosis of severe acute malnutrition (SAM) were recruited within 48 hours of admission. We excluded children who were suspected or confirmed to have cancer, congenital and chromosomal disorders like Down's syndrome, heart diseases, ataxia telangiectasia, cerebral palsy and metabolic disorders.

Study procedures

Anthropometry was carried out on all the children using standard and calibrated weighing scales, stadiometers and MUAC tapes appropriate for age. To ensure quality control instruments were calibrated daily and the scale was returned to zero before weight of the next patient was taken. Weights, height, MUAC were measured according to WHO standard procedures. All children who were found to have SAM had an HIV antibody test if they were above 18months those below 18 months had DNA PCR done. All caregivers consented on behalf of the children and a standard pretested questionnaire was administered to capture the social demographics, clinical history and clinical examination findings of the children. A sputum aspirate and gene x-pert and culture were performed. All children enrolled into the study received a tuberculin test and a chest x-ray. The data was captured using EPI DATA into a database by single entry and then exported into STATA version 13 for cleaning, coding and analysis. Descriptive statistics were analysed using frequencies, proportions, means and medians. The data was displayed in tables. Ethical approval was sought from Makerere University School of Health Sciences Higher Degree Research and Ethics committee. Thereafter national approval was sought from the Uganda National Council of Science and Technology and Mulago Hospital Management through the department of paediatrics.

Statistical analysis

The data was captured using IBM SPSS statistics 11 into a database by single entry and then exported into STATA version 11 for cleaning, coding and analysis. Descriptive statistics were analysed using frequencies, proportions, means and medians. The data was displayed in tables. The prevalence of TB/HIV was then determined as a proportion with its 95% CI. The comparison of outcomes was between children with and without TB/HIV using the Chi sq. test or Fischer's exact test as appropriate for categorical variables.

At bivariate analysis the continuous variables was compared using the Student's t test. A p-value of < 0.05 was considered to be statistically significant. Factors found to have a p value of < 0.2 of significance was entered in a multi variate model analysed by logistic regression to determine the risk factors associated to TB/HIV co-infection.

Results

A total of 173 children were enrolled into the study, 111/173 (64%) recruited presented with SAM-NE (Figure 1-3), 57/173 (33%) were HIV positive and TB diagnosis was made in 58/173 (33.5%). Clinical diagnosis contributed 50/173 (86%). The children found to have a positive TB contact were 28/173 (16%) and only 6/28 (21%) of these children had started on IPT.

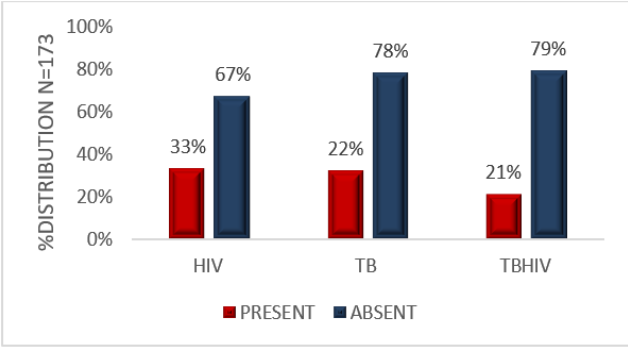

Figure 1: Is showing distribution of HIV, TB and TB/HIV co-infection among children admitted in Mulago hospital aged 1 - 5 years with severe acute malnutrition between November 2016 - April 2017.

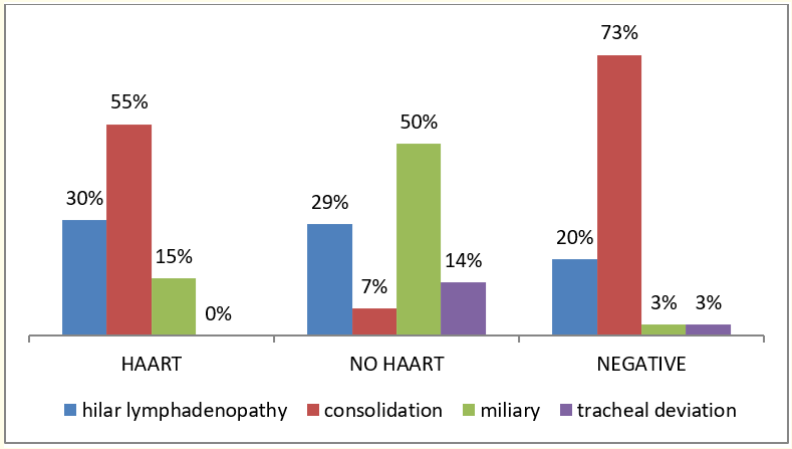

Figure 2: Showing different chest x-ray findings among children with SAM that were recruited into the study.

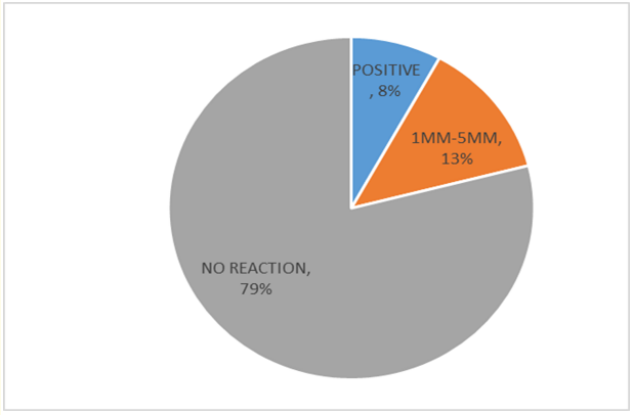

Figure 3: Pie chart showing TST findings among the study participants.

Prevalence of TB/HIV co-infection was 35/57 (61.4%) with only 53% of the HIV positive children on ART despite 83% of the children having known serology status at time of enrolment of the study. Of the 35 children diagnosed with TB/HIV co-infection, 11/35 (31%) had consolidation on chest x-ray and 10/35 (28%) had hilar lymphadenopathy.

Males contributed 57% of the total children enrolled and demonstrated a higher prevalence of TB and HIV infection of 57% and 66% respectively. Of the children 15/57 (26%) that were HIV positive had oedema and only 8/35 (23%) of the children with TB/HIV had oe-

dema. Oedema was more common in children found to have no TB and no HIV at 41/90 (44%).

Children recruited ranged from age 1 -5 years with a median age of 1.5 years, 69% of the children from urban areas. The children whose care takers had attained tertiary education did not have TB nor HIV infection. TB/HIV infection was highest in children whose caretakers were educated between primary and secondary each contributing 47% and 34% respectively of the children with co-infection.

HIV exposed but negative were 7/173 (4%) and 76/173 (44%) of the next of kin were not aware of their HIV status prior to enrolment of their children into the study 7% of these were HIV positive with a similar percentage of HIV positive children.17/173 (10%) of the recruited children had been admitted in the same month for malnutrition of whom 59% (10) had TB/HIV co-infection.

Twenty-seven children had positive TB contact 21/27 (77%) had exposure from their parents and only 7/27 (26%) had received IPT. Overall, 147/173 (85%) had completed their immunization. However, 26/173 (15%) had not completed their vaccination according to the Ugandan immunization schedule. The commonest vaccine that was not received was BCG among 18/26 (69%). The main reason for missing the BCG vaccine was noted to be lack of transport to the health facility.

Of the HIV positive children, 27/57 (43%) were ART naïve and only 23% were on CTX prophylaxis despite only 10/57 (18%) being newly diagnosed. IPT utilization among study participants that were HIV positive or had a positive TB contact was only 14% despite parents having been the commonest type of TB exposure at 22/28 (78%), 16/26 (62%) of the children with incomplete immunization were HIV positive.

Overall the commonest clinical presentation among the study participants was a history of cough and oral sores with 65% and 36% respectively. Only 32% were reported to have a positive history of fever while history of lymph node swelling occurred in only 9% (Table 1-4) Splenomegaly and hepatomegaly were the commonest finding on abdominal exam with 16% and 19% respectively.

Characteristics	Total number = 173 N (%)
Median age in years	1.5 (IQR: 1.2-2)*
Median weight in kg	7.2 (IQR: 6-8.8)**
Next of kin	
Mother	143 (83%)
Father	10 (6%)
Grandparent	10 (6%)
Aunt	10 (6%)
Type of residence	
Rural	53 (31%)
Urban	120 (69%)
Level of education	
None	24 (14%)
Primary	67 (39%)
Secondary	81 (47%)
Tertiary	1 (0.6%)

Type of employment of caretaker	
Casual	80 (46%)
Housewife	84 (49%)
Formal	9 (5%)
Caregiver awareness of HIV status	
Yes	76 (44%)
No	97 (56%)
Previous treatment for malnutrition	
Yes	17 (10%)
No	156 (90%)
Admission history in last one month	
Yes	46 (27%)
No	127 (73%)

Table 1: *The demographic characteristics of SAM children enrolled into the study between November 2016 and April 2017 in Mulago National Referral Hospital.*

**Indicates interquartile range of the age ** indicates interquartile range of the weight of children recruited into the study.*

Characteristics	Total number = 173 n (%)
HAART (n = 57)*	
Yes	30 (53%)
No	27 (47%)
CTX (n = 57)*	
Yes	23 (40%)
No	34 (60%)
Positive TB contact	
Yes	27 (16%)
No	146 (84%)
Type of contact	
Parent	21 (78%)
Neighbor	4 (14%)
Visitor	2 (8%)
Isoniazid prophylaxis (IPT) status (n = 69)*	
Yes	10 (14%)
No	59 (86%)
Immunization status	
Complete	147 (85%)
Incomplete	26 (15%)

Bacilli Calmette-Guerin (BCG) vaccine received	
Yes	156 (90%)
No	17 (10%)
History of fever	
Yes	56 (32%)
No	117 (68%)
History of cough	
Yes	113 (65%)
No	60 (35%)
History of oral sores	
Yes	63 (36%)
No	110 (64%)

Table 2: *Is illustrating the relevant history findings in SAM children recruited into the study during November 2016 to April 2017 admitted in Mulago National Referral Hospital.*

**Highlights variables whose total number of respondents < than 173.*

Characteristics	Total = 173 n (%)
Lymph node swellings	
Yes	15 (9%)
No	158 (91%)
Temperature	
Afebrile	51 (29%)
Febrile > 37.5	106 (61%)
Hypothermia < 35.0	16 (9.25%)
Finger clubbing	
Yes	10 (6%)
No	169 (94%)
Hepatomegaly	
Yes	33 (19%)
No	140 (81%)
Splenomegaly	
Yes	10 (6%)
No	163 (94%)

Table 3: *Is showing examination findings among SAM children recruited into the study during November 2016 - April 2017 that were admitted in Mulago Hospital.*

Characteristics N = 173	COR	P-Value	95%CI	AOR	P-Value	95%CI
Age	0.85	0.6	0.4-4.6	0.49	0.1	0.4-4.1
Type of malnutrition						
SAM-NE	1			1		
SAM-O	0.46	0.077	0.2-1.1	0.57	0.282	0.2-1.6
Next of Kin						
Mother	1			1		
Father	3.3	0.08	0.9-12.6	4.3	0.098	0.8-24
Grand Parent	5	0.017	1.3-18.5	4.6	0.063	0.9-22.9
Aunt	1.2	0.794	0.25-6.2	1.1	0.927	0.1-8
Positive TB contact						
Yes	12.1	<0.001	4.8-30.5	10.7	*<0.001**	3.6-32.4
No				0		
History of Admission						
Present	2.2	0.047	1-4.8	0.6	0.403	0.2-1.9
Absent				0		
BCG immunization						
Received	0.14	<0.001	0.6-0.4	0.2	*0.007**	0.07-0.65
Missed				0		
Temperature						
Febrile	1			2.68	0.164	0.7-10.8
Afebrile	1.55	0.353	0.6-3.9	0		
Hypothermia	4.89	0.014	1.4-17.4	10.7	*0.012**	1.7-67.5
Lymphadenopathy						
Present	12.2	<0.001	3.9-38.2	11.3	*0.002**	2.4-52.4
Absent	0			0		
Hepatomegaly						
Present	5.99	<0.001	2.6-13.8	6.21	*0.003**	1.9-20.1
Absent	0					
Respiratory distress						
Absent	0.35	0.03	0.13-0.9	0.4	0.16	0.1-1.4
Present	0.49	0.135	0.2-1.2	0.23	*0.036**	0,1-0.9
Oral Sores						
Absent	0			0		
Present	2.19	0.041	1.0-4.6	17.4	0.1	0.58-521

Table 4: *Showing multivariate analysis for factors associated with TB/HIV co-infection among children admitted with SAM in Mulago Hospital during November 2016 - April 2017.*

**Shows the statistically significant findings on multivariate analysis Factors at initial multivariate analysis that were associated with TB/HIV co-infection included a positive TB contact, missing of a BCG vaccine, hypothermia, presence of lymphadenopathy, hepatomegaly and absence of respiratory distress.*

A total of 44/173 (25%) x-rays done were found to be abnormal in line with the expected findings of pulmonary TB. The most frequent finding was consolidation, hilar lymphadenopathy and a miliary picture. Of the children with TB/HIV co-infection, 36% (12/33) had consolidation and 30% had hilar lymphadenopathy (10/33) and military TB respectively (10/33). Children on HAART and HIV negative presented similarly with consolidation and lymphadenopathy. The HIV positive children not on HAART presented with miliary TB x-ray.

Only 4% (7/173) of the gene x-pert tests were positive of the children tested using gastric aspirates. Of these 4 children were HIV positive and 3 was negative. Of the HIV negative 1 was sero-exposed and amongst the HIV positive children ¾ (75%) were on HAART.

A positive TST reading was found in only 8% (14/173) children of these 9/14(64%) were HIV negative. The children who were HIV positive and had a positive a TST reaction were all on HAART. A reading between 1-5mm was found in 22 children (13%) of these 17 (77%) were HIV positive and 65% were on HAART. 35/57(61%) of the children with HIV did not respond to the TST at all.

Discussion

TB/HIV co-infection among severely malnourished children was found to be 20.2%. When analysed among children who were HIV positive a prevalence of co-infection of 61.4% was found much higher than the country prevalence of co-infection of 43% [9]. A South African study which recruited only multi-drug resistant TB patients found TB/HIV co-infection rate at 77% among HIV positive children [33]. Our finding is similar to a post hoc analysis of 82 children admitted in Durban that reported a TB/HIV co-infection among SAM who were HAART naive to be 25.6% [21].

We found a history of positive TB exposure was highly associated with TB/HIV co-infection AOR 10.7 (95%, CI: 3.6 - 32.4), p value= < *0.001*. [23]. The duo immunosuppressive state of immature immune system and malnutrition places these children studied at a very high risk group for co-infection [34]. A positive history of TB contact has been found by several studies to be associated with an increased TB infection occurrence and these are in line with what we found in this study [27,35].

Our study found that in 77% of the children that reported a known TB contact; that contact was a parent. However, only 12% of the children that had a positive TB contact had been started on IPT indicating poor utilization and implementation of existing IPT guidelines by health workers. We may also postulate that TB contact tracing is not being optimally implemented as per guidelines of IPT and thus contributing to the low IPT utilization we found in our current study.

Children who had history of missing BCG vaccine had higher frequency of miliary TB 18% (4/22) compared to the children who had been immunized 5% (8/142). Our study demonstrated that while children still got TB despite BCG vaccination, they had a more localized form of TB infection. Seventy-one percent (12/17) of the children who presented with hilar lymphadenopathy had complete immunization even if they were HIV positive.

Our study found that children who presented with hypothermia were 4.9 times more likely to have TB/HIV co-infection with an AOR 10.7, (95%, CI: 1.7 - 67.5), p value = 0.012 compared to febrile children or afebrile children. Our study is the first large study to report such findings. However, a case report on an adult prisoner who presented with hypothermia was found to have TB meningitis [37]. On post-mortem he was found to have TB granulomas in the basal ganglia. It is hypothesized that the hypothermia was due to the TB granu-

loma depositions affecting temperature control and thus resulting into hypothermia. Our study found that all the children who had TB meningitis had hypothermia. It is therefore possible that these children had TB basal ganglia disease. However, malnutrition is known to cause hypothermia [41]. More studies need to be done around this finding to further quantify this association.

Though our study found only 15/58 (26%) of the children to have lymphadenopathy in whom 11/35 (31%) TB/HIV co-infection, this was significant with AOR 11.8, (95%, CI: 2.4 - 52.4), p-value 0.002. Other studies had similar findings of lymphadenopathy to be associated with TB/HIV co-infection [28].

In our study we found tachypnoea to reduce the risk of having TB/HIV where the AOR 0.23, (95% CI: 0.1 - 0.9), p value = 0.036 [28], which was a similar finding in this study where it was that stated dyspnoea to be rare in HIV positive children but could be a presentation in children with no HIV or malnutrition. Only 32% [20] HIV infected children presented with tachypnoea while 60 (53.5%) HIV negative children had distress of whom 26 had a diagnosis of TB made. We also found that a child presenting with tachypnoea was very unlikely to have TB/HIV infection.

We found hepatomegaly to be highly significant in children with TB/HIV co-infection with an AOR 6.21, (95% CI: 1.9 - 20.1), p value = 0.003 and this was in line with a study in Trinidad that found that HIV positive malnourished children usually presented with non-edematous malnutrition, oral sores and oral candidiasis, skin lesions and hepatomegaly and lymphadenopathy than in the HIV negative children as was noted in our study [38].

Since our study population was severely malnourished which in HIV is an AIDs defining illness, it is possible that the hepatomegaly could have been due to miliary TB, Hepatitis B/C, cytomegalovirus, atypical mycobacterium and other opportunistic infections that we couldn't screen for.

Limitations of the Study

Our study limitations were limited funding and we were therefore unable to carry out the following:

- HIV viral loads for the HIV infected participants and their CD4+ T cell counts.
- Sputum culture and microscopy for acid fast bacteria.
- Urine LAM to confirm TB infection.

Conclusion

- The prevalence of TB/HIV co-infection among severely malnourished children was very high at 20.2%.
- The factors associated with TB/HIV co-infection in SAM children were a positive history of TB contact, no BCG immunization, and presence of hypothermia, lymphadenopathy and hepatomegaly at multivariate analysis.

Recommendations

- Our study showed that there was reduced uptake of HAART among children admitted for SAM at 53% with even lower utilization of IPT amongst children who have known exposure to TB contact. Therefore, there is an urgent need to strengthen the implementation of available guidelines on screening and initiation of TB, HIV treatment.
- High index of suspicion for TB/HIV co-infection among SAM children presenting with history of missing BCG vaccine, a positive TB contact and clinical findings of hepatomegaly, lymphadenopathy, hypothermia, no respiratory distress and chest x-ray findings of consolidation and hilar lymphadenopathy should be entertained especially given the difficulty in diagnosis of tuberculosis in children.

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