

**Severe malnutrition with and without HIV-1 infection in hospitalised children in
Kampala, Uganda: differences in clinical features, haematological findings and CD4⁺
cell count**

*Hanifa Bachou MD, MPhil,^{1,2} Thorkild Tylleskär MD, PhD,² Robert Downing PhD,³ James K
Tumwine MD, PhD¹*

¹Department of Paediatrics and Child Health Makerere University Medical School P O Box
7072; Tel; +256-41-531875 Kampala Uganda, E-mail: sab@utlonline.co.ug ;
jtumwine@imul.com

²Centre for International Health, University of Bergen, Norway,
E-mail: thorkild.tylleskar@cih.uib.no, hanifa.bachou@student.uib.no

³CDC/Uganda Virus Research Institute Research Collaboration, P O Box 49, Entebbe,
Uganda, Email: rqd6@CDC.gov

Corresponding author:

Dr Hanifa Bachou

hanifa.bachou@student.uib.no

Centre for International health, UIB

Armauer Hansen building, N-5021 Bergen

Phone: +47 55 975540; +47 55 976361

Fax: +47 55 974979

Abstract

Background: The aim of the study was to describe the clinical features of severely malnourished children, haematological, CD4⁺ and CD8⁺ cell counts in relation to HIV-infection. **Methods:** The study setting was the paediatric wards of Mulago hospital, Uganda's national referral and teaching hospital. This paper reports on 315 severely malnourished children (weight-for-height < -3 z-score or presence of oedema) studied. At admission, CD4⁺ and CD8⁺ cells were measured (FACScan) and HIV serology was confirmed (by ELISA) for those > 18 months, and RNA PCR for those ≤ 18 months. Complete blood count, including differential counts was done using a Beckman Coulter counter. **Results:** Of the 315 children, 119 (38%) were female; median age 17 months (IQR 12- 24); with no difference in HIV status by sex or age. The children had a high prevalence of infections: pneumonia (68%), diarrhoea (38%), urinary tract infection (26%) and bacteraemia (18%), with no significant difference by HIV status (HIV infected vs. HIV uninfected). However, HIV infected children were more likely as compared with HIV uninfected severely malnourished children to have persistent diarrhoea, odds ratio (OR 2.0, 95% CI 1.2-3.6). The median white blood cell count (8700 vs. 10700); and lymphocyte count (2687 vs. 4033), were significantly lower in HIV positive than HIV negative children. Children with non-oedematous malnutrition were more likely to have CD4⁺ percentages <15% (RR 4.2, 95% CI 1.4-13) and <20% (RR 3.1, 95% CI 1.5-6.5) when compared with children with oedematous malnutrition even after controlling for HIV infection. New in the study is the observation that both HIV-positive and HIV-negative children without oedema present with lower CD4⁺ percentages, compared to children with oedema. Both these observations seem to imply that the development of oedema requires a certain immuno-competence, which is an interesting clue to the pathophysiology of oedema in severe malnutrition

Introduction

Severe malnutrition has been associated with acquired immunodeficiency among children worldwide referred to as Nutritionally Acquired Immunodeficiency Syndrome or NAIDS [1, 2]. With the advent of the human immunodeficiency virus (HIV) pandemic, the role of malnutrition in immunodeficiency has tended to be overlooked, and indeed only a handful of studies have investigated CD4⁺ and CD8⁺ lymphocyte subsets in severely malnourished children [3, 4].

There is little information on the effect of the added burden of HIV-infection on the clinical features [5-7] and cellular immunity of severely malnourished children. The objective of this study was to describe the clinical features, haematological, CD4⁺ and CD8⁺ lymphocyte subsets of severely malnourished children by HIV status.

Subjects and methods

All severely malnourished children consecutively admitted to the paediatric wards of Mulago, Uganda's national referral and teaching hospital during two peak seasons for malnutrition, September –November 2003 and September – December 2004 were followed up from admission to outcome (death or discharge). In all, 450 severely malnourished (weight-for-height of < -3 z- score and/or presence of oedema) below 60 months of age, whose parents or caregivers gave informed consent, were included in the study, figure 1. Risk factors for death in the first season (2003) have been published where more details of methodology can be found.

This paper reports on the 315 children with complete HIV test results, CD4, CD8 count and percentage results. The laboratory work-up was incomplete for 135 children due to lack of

reagents (89), inadequate blood volume (38), haemolysis (6) and not bled (2). We compared basic characteristics of the 315 children with complete results with the 135 with incomplete results.

We recorded the demographic characteristics (age, sex) and clinical features (presence of oedema, weight, height/length, diarrhoea), haematological tests (haemoglobin concentration, white blood cell count and differentials, presence of malaria parasites), HIV tests (ELISA and PCR), microbial tests (blood and urine culture and sensitivity), immunologic tests (CD4⁺ and CD8⁺ counts and percentages) and chest x-ray reports of the children. CD4⁺ and CD8⁺ cells were measured (FACScan) and HIV serology was confirmed (by ELISA) for those > 18 months, and RNA PCR for those ≤ 18 months. We used the CD4 percentage to categorize HIV. The clinical definition classifies all our patients into the category C as all of them were severely malnourished. The haemoglobin values were evaluated according to the WHO criteria :< 5 g/dL and < 4mg/dL are referred to as severe anaemia and very severe anaemia, respectively.

Laboratory methods

Blood was taken in a 5 ml EDTA vacutainer tubes (Becton Dickinson, Franklin lakes, NJ USA) in the mornings between 8 -11 am by venipuncture and transported within 4 hours to Uganda Virus Research Institute (UVRI) laboratory, Entebbe for serological testing. HIV testing was performed using standard HIV algorithm of two enzyme-linked immunoassays (EIA) in parallel. Western blot, realtime polymerase chain reaction (RT-PCR) was performed to confirm a positive EIA test for children below the 18 months old and children with indeterminate results on EIA.

TriTEST reagents (CD3; FITC/CD4; PE/CD45; PerCP and CD3; FITC/CD8; PE/CD45; PerCP) were used to stain PBMC for CD4⁺/CD8⁺ cell counting in line with the manufacturer's instructions. FACSscan instrument and MultiSET software were used to perform flow cytometry and report the absolute CD4⁺ and CD8⁺ cell counts for each specimen using dual-platform approach (Becton Dickinson, Franklin lakes, NJ USA). Complete blood count, including differential counts was done using a Beckman Coulter counter [8]. Blood was stained within 12 hours of collection and results analysed within 24 hours.

Severe malnutrition was defined according to the WHO classification, and severe wasting (weight for height < 3 SD of the NCHS/WHO reference values with no oedema) and/or oedematous malnutrition (presence of symmetrical oedema involving at least the feet) [9]. The children were divided in two groups, HIV-infected and non-infected.

The study protocol was approved by the Regional Committee for Medical Ethics, Bergen, Norway (REK Vest), Makerere University Faculty of Medicine Ethics and Research Committee, Mulago Hospital Ethics Committee and the Uganda National Council for Science and Technology.

Statistical analysis was done using SPSS version 13. Medians were used to measure central tendency and inter quartile range (IQR) for the spread of haemoglobin concentration, leucocytes (WBC), total lymphocytes, CD4⁺ and CD8⁺ cell counts. Children were grouped by their gender (male, female), age groups in months (≤ 24 months and > 24 months), presence of oedematous malnutrition and HIV infection, CD4⁺ levels (CD4⁺-cell % < 20%, and CD4⁺-cell % < 15%). Chi square and Wilcoxon-Mann-Whitney tests and multivariate analysis were used to test for differences by HIV status and gender and type of severe malnutrition (oedematous

vs. non-oedematous) A 2- tailed p-value of < 0.05 was considered significant. Binary logistic regression models were built with HIV status as outcome variable. Important baseline data of clinical significance found appropriate was included in a regression model and used for adjustment. Variables were also chosen according to their statistical significance ($P < 0.05$) using Chi-square. Dummy variables were created for categorical variables used. Chosen dependent variables were tested for interactions and very significant variables were stratified for possibility of effect modification. Positive interactions remained in the final model. Independent variables that showed persistently non-significant relationship with the dependant variable during modelling were excluded from the final model.

Results

Of the 315 children, 119 (38%) were female and the median age was 17.0 months (IQR 12 – 24). Half the children were between 12-24 months old and a few (3%) were below 6 months, table 1. The age distribution was not affected by their HIV status. Almost half, (170/315) had oedematous malnutrition (kwashiorkor and marasmic-kwashiorkor). These characteristics (sex, age, type of malnutrition) were comparable to those of the 135 children with incomplete laboratory data.

Almost 40% (123/315) were HIV infected. The HIV infected children were less likely to present with oedema (OR 0.5 (95% CI 0.3 – 0.7)). Only 27 (9%) of the severely malnourished children had no identifiable infection on admission, 51 (16%) had one type of infection and the majority, 227 (72 %) had more than one type of infection on admission. The infections included pneumonia (68%), diarrhoea (38%), urinary tract infection (26%), bacteraemia (18%), malaria (9%) and oral thrush (11%), (Table 2). Overall, there was no significant difference in the prevalence of infection by HIV status. However, HIV-1 infected children were more likely to have persistent diarrhoea and oral thrush (Table 2).

The median haemoglobin concentration of these children was below 9 g/dL. There was no significant difference in levels of haemoglobin concentration by type of severe malnutrition or HIV status, (Table 3). The total white blood cell count was significantly lower in HIV positive than HIV negative children 8.9×10^6 (IQR 5.4 –11.3) versus 9.1×10^6 (7.2 –13.5), ($p=0.028$). In HIV infected children, the total white blood cell count was lower in the non-oedematous compared to oedematous children. However, this difference was not observed among the uninfected children (Table 4).

The total lymphocyte counts were 2.9×10^9 (IQR 2.0 – 4.9) for HIV positive and 4.5×10^9 (IQR 2.9 – 6.3) for uninfected children, ($p=0.008$). Absolute lymphocyte counts were 2.7×10^9 (IQR 1.8 – 4.9) for HIV infected and 4.0×10^9 (2.8 – 5.6) for uninfected children, ($p<0.001$). HIV infected children with non-oedematous had lower total lymphocyte, monocyte, and neutrophil counts than those with oedema. This was not observed amongst the uninfected children.

The differences by HIV status were both significant, $p<0.001$. Regardless of their HIV status, children with severe non-oedematous malnutrition (marasmus) had significantly lower $CD4^+$ count, $CD4^+$ and $CD8^+$ percentages and $CD4^+ / CD8^+$ ratios than those with oedematous malnutrition (kwashiorkor and marasmic-kwashiorkor), (Table 4, Figure 2)

One third of the 315 severely malnourished children had $CD4^+$ cell count percentage below 25%. Of these, 17% (55/315) had $CD4^+$ percentage below 15 – 24 %, indicative of moderate cellular immuno-suppression while 18% had $CD4^+$ percentage below 15 % indicative of severe cellular immuno-suppression. Both categories of cellular immuno-suppression were in both the HIV infected and HIV uninfected groups, (table 5). Children with non oedematous malnutrition were more likely to have $CD4^+$ percentages below 15%, (OR 4.2, CI 1.4-12.6); and between 15 – 25 %, (OR 2.0, CI 0.6 – 6.8) than children with oedema. This difference persisted even after controlling for their HIV status, (figure 2).

Discussion

In this study we have studied an old problem - severe malnutrition in children - with the modern techniques for assessing immuno-competence that has developed over the last decades in response to the HIV/AIDS pandemic. We have used the up-to-date laboratory techniques for the assessment lymphocyte subsets in recognised laboratories. Because some of the severely malnourished children are also HIV-positive we can now describe the clinical and laboratory features of these two groups of patients: severely malnourished children, with or without HIV. We notice the well known fact that the clinical features of severe malnutrition and that of HIV/AIDS are overlapping in young children. This affects the possibility of an accurate clinical diagnosis of HIV infection in resource-poor settings where there is co-existence of the two diseases, often with inadequate HIV testing facilities [16]. So, are there any clinical differences allowing to suspect HIV in severe malnutrition?

In our study in Uganda, both groups of children had a high prevalence of multiple infections including pneumonia, diarrhoea, bacteraemia, malaria, urinary tract infection and oral thrush. For respiratory infections, blood stream infections or urinary tract infections, no significant difference was observed by HIV status. The only two conditions that were overrepresented among the HIV-infected children were persistent diarrhoea and oral thrush. In view of the marked difficulties differentiating the two clinically, we strongly support the establishment of routine counselling and testing for HIV-1 among paediatric patients with severe malnutrition in settings where HIV is a problem. An observation in our study is that there was a high acceptability of counselling and testing for HIV-1 in this setting, another reason not to hesitate to organise routine counselling and testing for HIV-1. also in the paediatric setting.

The drop-outs in the study were mostly due to random factors and we do not think this affected the selection study subjects in any systematic way. In addition, the 315 of the 450

severely malnourished children that were analysed had the same basic characteristics as the drop-outs.

The median CD4⁺ cell counts and percentages were compared to the recently published median CD4⁺ count and percentage of healthy Ugandan children younger than five years [18]. Among the HIV uninfected children without oedema, as many as one third of them had signs of immunosuppression with a CD4⁺ percentage below 25%. For the HIV uninfected with oedema, it was one in twelve. For the HIV infected children without oedema, almost 80% had signs of immunosuppression in the form of CD4⁺ percent below 25%. For the HIV infected with oedema, about half the children had CD4⁺ below 25%. Very low levels of CD4⁺ cell percentages consistent with a laboratory diagnosis of AIDS have rarely been described in HIV uninfected children with or without mixed infections. Reports on proportions of T cells % and CD4⁺ cell percentage in severely malnourished children are inconsistent [3, 4, 19, 20]. The difference observed may be influenced by difference in study designs and sample size.

Alterations in haematological functions in malnutrition have been documented [17]. A recent study reported 5 malnourished children with mixed infection who had a higher monocyte count than the 4 with only respiratory infection although their HIV status was not reported [3]. Therefore, both granulocyte and lymphocyte suppression observed in this study is an indication of reduced haemopoietic function and the additional burden of HIV-1 infection seems to further reduce this function.

CD4⁺ cells percentages in this study were lower in children who presented with non oedematous severe malnutrition and remained consistent in both the HIV infected and non infected groups. Earlier studies reported that oedematous malnutrition had lower T cells [19], [21], while others found no difference by type of malnutrition [4]. The reason for these controversies is not clear. All we know is that severe malnutrition alters immunological

competence through a number of mechanisms including apoptosis of the thymus gland [22, 23] and micronutrient deficiencies[24]. Likewise, the rapid destruction of CD4 T-lymphocytes by the HIV-1 virus has been well established. However, mechanisms leading to cellular immunological alterations in co-existing state of severe malnutrition and HIV-1 virus infection are not yet clear.

It is interesting to notice that HIV-positive children less often present with oedema, just over 40% compared with over 60% among the HIV-negative children. Severe wasting in the absence of oedema is a common feature observed in severe malnutrition with concurrent HIV infection [6, 11, 13-15]. New in this study is the observation that both HIV-positive and HIV-negative children without oedema presents with lower CD4+ percentages, compared to children with oedema. Both these observations seem to imply that the development of oedema requires a certain immuno-competence, which is an interesting clue to the pathophysiology of oedema in severe malnutrition

Conclusion

Severe protein energy malnutrition is associated with depletion of haematological and lymphocyte subsets exacerbated by the presence of HIV 1 infection. Cell mediated immuno-suppression is more marked in non-oedematous severe malnutrition regardless of HIV status.

Authors' contributions

All authors participated in the design of the study, interpretation of the results, statistical analysis and writing the manuscript. HB supervised patient recruitment, follow-up and data collection. All authors read and approved the final manuscript.

Competing interests

We declare that we have no competing interests.

Acknowledgements

We acknowledge financial support from the NUFU project (Essential Nutrition and child health) collaboration between the Department of Paediatrics and Child Health, Makerere University, Kampala, Uganda and the Centre for International Health, University of Bergen Norway; NORAD and the Norwegian government Quota Program. Thanks to the research assistants for their invaluable help.

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Figure legends

Figure 1. Study profile showing the enrolment process of the 315 children in the study.

Figure 2. Box and whisker plot showing the median, interquartile and range of CD4⁺ percentage of lymphocytes of severely malnourished children by HIV status and type of malnutrition

Table 1. Characteristics of the 315 children below 60 months of age with severe malnutrition admitted to Mulago hospital, Uganda, in the two peak periods for malnutrition 2003-2004.

Age group Months	HIV-infected n=123		HIV-uninfected n=192		Total
	Male	Female	Male	Female	
0 – 5.9	1	2	4	4	11
6 – 11.9	15	8	21	14	58
12 – 23.9	36	21	66	37	160
24 – 35.9	17	8	19	6	50
36 – 47.9	4	4	6	6	20
48 – 59.9	2	5	5	4	16
Total	75	48	121	71	315

Table 2. Characteristics, medical conditions and diagnosis of children below 60 months of age with severe malnutrition, Mulago hospital, Uganda.

	HIV- infected n (%)	HIV- uninfected n (%)	Odds ratio (95% CI)
Symptoms and signs	<i>(n=123)</i>	<i>(n=192)</i>	
Diarrhoea (all)	52 (42)	67 (35)	1.4 (0.9 – 2.2)
Persistent diarrhoea (> 2weeks)	32 (26)	28 (15)	2.1 (1.1 – 3.8)*
Oral thrush	20 (16)	15 (8)	2.3 (1.1 – 4.7)*
Bilateral oedema (nutritional)	53 (43)	119 (62)	0.5 (0.3 – 0.7)*
Severe dehydration	7 (6)	11 (6)	1.0 (0.4 – 2.7)
Chest x ray findings	<i>(n=109)</i>	<i>(n=158)</i>	
Bronchopneumonia	26 (24)	48 (30)	0.7 (0.4 – 1.3)
Interstitial Pneumonia	40 (37)	48 (30)	1.3 (0.8 – 2.2)
Suspected tuberculosis	14 (13)	18 (11)	1.2 (0.5 – 2.4)
Blood tests	<i>(n=122)</i>	<i>(n=191)</i>	
Malaria parasites	10 (9)	19 (11)	0.9 (0.4 – 1.9)
Severe anaemia (Hb<5 g/dL)	10 (8)	2 (6)	1.3 (0.6 – 3.3)
Bacteraemia	24 (20)	32 (17)	1.2 (0.7 – 2.2)
Urine tests	<i>(n=109)</i>	<i>(n=160)</i>	
Bacteruria	33 (30)	36 (23)	1.5 (0.9 – 2.6)

* Statistically significant

Table 3. The medians and interquartile ranges of haemoglobin levels, total white blood counts (WBC) and differentials, CD4⁺ and CD8⁺ cell counts, percentages and ratios of all the 315 severely malnourished children below 60 months of age, by their HIV status.

	HIV-infected median (IQR) n = 123	HIV-uninfected median (IQR) n =192
Haemoglobin	7.8 (6.4 – 9.2)	8.1 (6.5 – 9.6)
Total WBC (10 ⁹ /L)	8.9 (5.4 – 11.3)	9.1 (7.2 – 13.5)**
Neutrophils (10 ⁹ /L)	4.9 (2.8 – 8.0)	5.9 (3.4 – 8.9)
Neutrophils (%)	59 (35 – 71)	55 (41 – 65)
Monocytes (10 ⁹ /L)	0.22 (0.11 – 0.94)	0.28 (0.15– 0.53)
Monocytes (%)	2 (1.8 – 7.5)	2 (1.8 – 5)
Total lymphocytes (10 ⁹ /L)	2.9 (2.1 – 4.9)	4.5 (2.9 – 6.3)**
Lymphocytes (%)	39 (26 – 50)	40 (32 – 50)
CD4 ⁺ cell count (10 ⁶ /L)	497 (280 – 1379)	1265 (829 – 1758)***
CD4 ⁺ cells %	18 (12 – 34)	33 (26 – 40)***
CD8 ⁺ cell count (10 ⁶ /L)	880 (490 – 1750)	588 (331 – 913)***
CD8 ⁺ cells %	31 (23 – 50)	15 (13 – 21)***
CD4 ⁺ / CD8 ⁺ ratio	0.76 (0.24 – 1.19)	2.0 (1.5 – 2.8)***

*p<0.05, ** p< 0.01, *** p<0.001

Table 4. The medians and interquartile ranges of haemoglobin levels, white blood counts and differentials, CD4⁺ and CD8⁺ cell counts, percentages and ratios of all the 315 severely malnourished children below 60 months of age, by their HIV status and type of malnutrition

	HIV-Infected		HIV-uninfected	
	Oedema	No oedema	Oedema	No oedema
	n = 53 median (IQR)	n = 70 median (IQR)	n =119 median (IQR)	n =73 median (IQR)
Haemoglobin g/dL	8.2 (6.4–9.6)	7.3 (6–9.1)	8.0 (6.1–9.3)	8.4 (6.7–9.8)
White blood cells(10 ⁹ /L)	11.0 (8.3–17)	7.2 (4.2–12)	10.0 (7.7–17)	11.0 (8.8–15)
Neutrophils (10 ⁹ /L)	6.2 (3.1–8.5) *	2.9 (2.3–7.7)	5.4 (3.5–8.8)	6.1 (3.2–9.0)
Neutrophils (%)	59.0 (34–70)	61.0 (37–73)	55.0 (48–66)	53.0 (38–63)
Monocytes (10 ⁹ /L)	667.0 (182–1246) *	153.0 (83–263)	217.0 (107–540)	412.0 (176–534)
Monocytes (%)	5.7 (2–10)*	2.0 (1.0–2.8)	2.0 (1–5)	3.5 (2–6.5)
Total lymphocytes(10 ⁹ /L	3.3 (2.4–6.3)	2.5 (1.7–4.1)*	4.5 (2.6–7.2)	4.4 (3.6–5.7)
Lymphocytes (%)	39.0 (23–57)	36.0 (26–50)	39.0 (31–49)	42.0 (32–55)
CD4 ⁺ cell count	630.0 (305–1759)***	379.0 (123–713)	1354 (894–1914)***	1169 (682–1600)
CD4 ⁺ cell %	20.0 (14–42)***	14.0 (5–25)	35.0 (29–44)***	27.0 (22–37)
CD8 ⁺ cell count	1046 (521–1896)	811.0(462–1363)	822.0 (492–1367)*	595 (328–1054)
CD8 ⁺ cell %	23.0 (20–39)*	41.0 (27–56)	15.0 (12 –21)	16.0 (13–21)
CD4 ⁺ / CD8 ⁺ ratio	0.9 (0.4 –1.6)***	0.4 (0.1–0.9)	2.2 (1.6–3.0)	1.9 (1.2 –2.8)

* p- value < 0.05 ** p-value <0.005 *** p-value < 0.001, comparing each HIV status group with type of severe malnutrition.

Table 5. Distribution of the 315 severely malnourished children by type of severe malnutrition their cellular immunological category and HIV status.

	HIV-infected n (%)	HIV-uninfected n (%)	Total
Oedema	n=53	n=119	N=172
CD4 ⁺ ≥ 25%*	28 (53)	119 (100)	171 (99)
CD4 ⁺ 15 – 24%**	15 (28)	0 (0)	0 (0)
CD4 ⁺ < 15%***	10 (19)	0 (0)	1 (1)
No oedema	n=70	n=73	N=143
CD4 ⁺ ≥ 25%*	15 (21)	50 (69)	65 (45)
CD4 ⁺ 15 – 24%**	22 (31)	15 (20)	37 (26)
CD4 ⁺ < 15%***	33(62)	8 (11)	41 (29)

*No evidence of suppression, ** Evidence of moderate suppression, *** Severe suppression

Figure 1

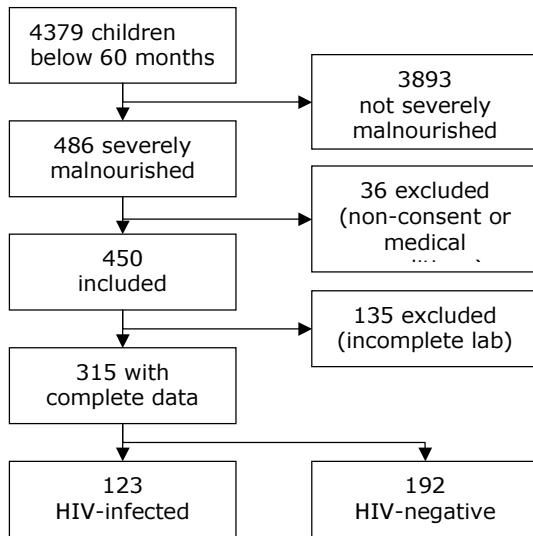


Figure2

