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EVALUATION OF A PROPOSED CLINICAL CASE DEFINITION OF PAEDIATRIC ACQUIRED IMMUNE DEFICIENCY SYNDROME

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ABSTRACT

Objective: **To evaluate the proposed criteria against the laboratory parameters and to identify the clinical features with the highest predictive value in the diagnosis of paediatric AIDS.**
Design: **A cross sectional study.**
Setting: **Kenyatta National Hospital, Nairobi.**
Results: **More than twenty three per cent of the children studied were seropositive and 14% were diagnosed as having AIDS. Almost 70% of the children studied were below 24 months. AIDS was significantly associated with mouth lesions, both ulcers and oral candidiasis, skin lesions especially eczema and generalised pruritic dermatitis, prolonged cough, prolonged fever and generalised lymphadenopathy. The WHO criteria had a sensitivity of 60%, a specificity of 94%, positive predictive value of 60%, and negative predictive value of 94%. The Nairobi diagnostic criteria had a sensitivity of 80%, a specificity of 79%, a positive predictive value of 38% and a negative predictive value of 96%.**
Conclusion: **The Nairobi Diagnostic Criteria are superior to the WHO criteria as a screening test due to their higher sensitivity, 80% against 60% for WHO.**

INTRODUCTION

Paediatric HIV infection and its complications are currently the commonest cause of hospital admissions in most hospitals in sub-Saharan Africa. At birth, only a very low proportion of children have signs of infection, but by one year 80-90% will have manifested with some features of infection. AIDS is diagnosed in 30% of infants in the first year of life and this number progressively increases so that by the fifth year of life, 75% of HIV infected children have died(1-5).

HIV- 1 disease in children presents with a wide spectrum of symptoms and clinical findings that depend on the disease stage. Clinical features useful in recognition of paediatric AIDS have many shared features with common diseases of infancy and childhood in the developing countries. However, in HIV infected subjects the symptomatology tends to be more severe and protracted. Clinical presentations that have been described in African cohorts mainly include persistent cough, chronic diarrhoea and prolonged fever, weight loss or failure to thrive, persistent generalised lymphadenopathy, oral candidiasis, and chronic pruritic dermatitis(6,7).

Most children with HIV infection present to hospital when they already have symptomatic disease or AIDS. The medical management of these children is compounded by the occurrence of opportunistic infections, which require prompt and aggressive treatment to improve survival. This is dependent on making an accurate diagnosis of HIV infection. However, in most hospitals in the sub-Saharan region making a definitive laboratory diagnosis of HIV infection before the age of 15 months is often only possible in research laboratories. As a result clinicians have had to rely on the use of a clinical criteria initially developed for surveillance to make a diagnosis of HIV infection in children (WHO)(8).

These clinical criteria have been evaluated in a number of studies and have been found to have unacceptably low sensitivity in children due to similarities between paediatric AIDS with other prevalent clinical entities. In a study conducted in a paediatric department in Mama Yemo Hospital, Zaire, the WHO criteria was tested on 159 children. It was found to be specific (87%) but lacked sensitivity (35%) and positive predictive value (25%)(9,10). Similar evaluations were carried out on 177 hospitalised children in Kampala and on 221 children in Kigali, Rwanda(11,12). Specificity was found to be high (92%) in both studies. However, sensitivity and positive predictive value were low in both Kampala and Kigali (41% and 48%, respectively). These findings emphasise the difficulties of diagnosing AIDS in children using clinical criteria and ELISA seropositivity. In Belgium, in a paediatric department, the WHO criteria were compared to the Center for Disease Control Case definition 3rd revision. The WHO criteria was found to have a low sensitivity (58%), and a high specificity (92%)(13).

This study was undertaken to evaluate a modified clinical criteria for paediatric AIDS that was developed with an aim of improving the sensitivity of the existing WHO clinical criteria (appendix 1).

MATERIALS AND METHODS

The modified WHO clinical criteria termed the Nairobi diagnostic criteria (appendix 2) was formulated through a process of consultation and consensus building with five senior clinicians at the hospital with experience in the management of children with paediatric AIDS.

This cross sectional study was undertaken in the Paediatric General Wards of the Kenyatta National Hospital (KNH) in November and December 1992. KNH is the national referral hospital in Kenya with a bed capacity of about 1860 of which 335 are general paediatric beds. All children aged 0-12 years admitted in paediatric wards were eligible for inclusion into the study if their parents gave consent and if they had not been on any immunosuppressive therapy such as cytotoxic drugs or steroids. A systematic selection of cases was done by taking every third child admitted to the paediatric service. At admission a medical history was obtained and a physical examination carried out by the investigators. The information obtained was recorded in a pre-coded questionnaire, which addressed all the elements of both the proposed Nairobi diagnostic criteria and the WHO clinical case definition.

After pre-test counselling, a sample of peripheral venous blood was drawn from both mother (1 ml) and child (0.5 ml) for HIV-1 serology. Two ELISA screening tests were carried out using a commercially available ELISA kit by IAF - Biochem. All reactive samples were subjected to a third ELISA by Recombigen Biochem as a confirmatory test. For all positive samples in the child, fresh samples of 0.5 mls were collected in a bottle with tripotassium EDTA for lymphocyte analysis (CD4+ and CD8+ counts).

The gold standard for the diagnosis of AIDS in this study was defined as ELISA HIV-1 seropositivity plus a CD4+/CD8+ ratio < 0.6, where 0.6 lies on the 3rd centile for age adjusted ratio(12). Children who attained the gold standard were said to have AIDS.

All the clinical and laboratory data were entered in a computer using the SPSS/DE program. Data was summarised in frequency tables. Two by two contingency tables were drawn for the WHO and the Nairobi Diagnostic criteria. Sensitivity, specificity, negative and positive predictive values were calculated for both the proposed Nairobi diagnostic criteria and the WHO criteria. Dichotomous variables were analysed using the Chi-square test or Fisher's exact test where appropriate. Multiple logistic regression analysis was used to determine the clinical manifestations with the highest predictive value for paediatric AIDS. The level of statistical significance was taken at 0.05.

RESULTS

A total number of 156 children were enrolled in the study with a median age of 16 months (range 0.5 to 144 months), 68.1% of the children were below the age of 24 months. The HIV seroprevalence rate among the study population was 23%. Lymphocyte analysis was done in 23 of 36 (64%) HIV-1 seropositive children. Children without results for lymphocyte analysis were excluded from further analysis. Of the children who were HIV-1 seropositive 87% (20/23) were diagnosed as having AIDS using the gold standard. The median age of children with AIDS was 18 months (range 3- 72 months). Seventy five per cent of the children with AIDS were less than 24 months old. Their age and sex distribution is shown in Table 1.

Table 1

Age and sex distribution of children with AIDS

Age (months)	Male No. (%)	Female No. (%)
0 - 12	2 (10.0)	5 (25.0)
13 - 24	2 (10.0)	6 (30.0)
25 - 36	0 (0.0)	1 (5.0)
> 36	4 (20.0)	0 (0.0)
Total	8 (40.0)	12 (60.0)

Table 2 shows the distribution of past history and symptoms of various clinical entities, and the association with AIDS. Children with AIDS were more likely to have had a prior admission (p=0.05), and were significantly more likely to have a history of previous oral lesions (p<0.0001), itchy skin rash (p=0.01), ear discharge (p=0.02) and retarded milestones (p=0.03). Children with AIDS presented with similar symptoms to those without AIDS. However, children with AIDS were significantly more likely to present with longer duration of symptoms such as cough (p<0.0001), fever (p<0.0001), vomiting (p=0.03), lethargy (p=0.005) and poor feeding (p=0.01).

On physical examination children with AIDS were significantly more likely to have generalised lymphadenopathy (OR 6.8, 95% CI 1.9-24.7) oral ulceration (OR 3.0, 95% CI 0.9-9.3), oral candidiasis (OR 7.4, 95% CI 2.3-24.6), lethargy (OR 1.9, 95% CI 1.3-12.8), irritability (OR 1.8, 95% CI 1.2-11.1) and wasting (OR 4.5, 95% CI 1.4-14.2) (Table 3).

The sensitivity, specificity and predictive values of various clinical features for AIDS are shown in Table 4. Prolonged cough (>4 weeks) (71%), failure to gain weight or weight loss, (80%), and mouth ulcers (80%), were the three most sensitive clinical indicators of AIDS. Whereas oral thrush (90%), prolonged fever (95%) and generalised lymphadenopathy (93%) had the highest specificity for AIDS.

Table 2

Distribution of clinical characteristics in children with and without AIDS

Clinical characteristic	AIDS (n = 23) No. (%)	No AIDS (n = 123) No. (%)	P value
Past medical history			
Previous admissions	11 (55.0)	37 (30.0)	0.05
Mouth lesions	16 (80)	34 (27.6)	<0.0001
Skin rash	13 (65.0)	42 (34.1)	0.02
Itchy dermatitis	12 (29.4)	18 (47.3)	0.01
Ear discharge	7 (35)	14 (11.4)	0.02
Retarded milestone	8 (44.4)	22 (18.5)	0.03
Abnormal behaviour	4 (20)	6 (4.9)	0.05
Apathy	4 (100)	1 (16.7)	0.05
Presenting symptoms			
Cough	17 (85)	91 (74)	0.4
Fever	13 (68.4)	80 (66.7)	1.0
Diarrhoea	13 (65)	49 (39.8)	0.06
Vomiting	12 (60)	57 (46.3)	0.26
Poor appetite	15 (78.9)	77 (62.6)	0.26
Convulsion	0 (0)	20 (16.3)	0.11
Failure to thrive/weight loss	16 (80.0)	58 (47.2)	0.01
Skin rash	13 (65.0)	23 (18.9)	<0.0001
Mouth lesions	12 (60.0)	27 (22.1)	0.001
Duration of symptoms			
Cough >1 month	12 (70.6)	12 (13.5)	<0.0001
Fever >1 month	7 (53.8)	4 (5.0)	<0.0001
Vomiting >1 month	7 (58.3)	12 (21.4)	0.03
Lethargy >1 month	9 (56.3)	12 (18.2)	0.005
Poor appetite >2 weeks	8 (53.3)	13 (17.8)	0.009
Diarrhoea >2 weeks	8 (61 .5)	15 (46.9)	0.05

Various risk factors associated with AIDS were studied. These were history of blood transfusion, number of transfusions in units, circumcision and tooth extraction by traditional healers, history of sexual abuse and history of injections. None of these risk factors were significantly associated with AIDS.

Table 3

Distribution of clinical signs in association with AIDS

Physical finding	AIDS (n=20) No. (%)	No AIDS (n=123) No. (%)	Odds ratio (95% CI)	P value
Generalised lymphadenopathy	7 (35.0)	9 (7.3)	6.8 (1.9-24.7)	0.001
Oral ulcers	8 (40.0)	22 (17.9)	3.0 (0.1-9.3)	0.05
Oral candidiasis	9 (45.0)	12 (9.9)	7.4 (2.3-24.6)	0.0002
Lethargy	14 (70.0)	45 (36.6)	1.9 (1.3-12.8)	0.01
Irritability	14 (70.0)	49 (39.8)	1.8 (1.2-11.1)	0.02
Wasting	8 (40.0)	16 (13.0)	4.5 (1.4-14.1)	0.008
Temperature >37.5°C	7 (36.8)	50 (44.6)	1.4 (0.5-4.2)	0.7
Pallor	8 (40.0)	30 (24.6)	2.0 (0.7-6.0)	0.2
Reduced level of consciousness	3 (15.0)	13 (10.6)	1.4 (0.15-33.7)	0.8
Parotid enlargement	2 (10.0)	2 (1.6)	6.7 (0.5-101.6)	0.1
Hepatomegaly	5 (25.0)	12 (9.8)	3.1 (0.8-11.2)	0.1
Splenomegaly	3 (15.0)	7 (5.7)	2.9 (0.4-14.3)	0.3

(95% CI = 95% confidence interval)

Table 4

Selected clinical characteristics: their sensitivity, specificity, positive and negative predictive values in relation to AIDS.

Clinical characteristic	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
History of mouth lesions	80	72	32	96
History of ear discharge	35	89	33	89
Retarded milestones	44	82	27	91
Abnormal behaviour	20	95	40	88
Fever >1 month	54	95	63	93
Cough >1 month	71	87	50	94
Diarrhoea >1 month	32	39	65	14
Vomiting >1 month	58	79	37	90
Poor appetite >1 month	53	82	38	90
Lethargy >1 month	56	82	43	89
Failure to gain weight or loss of weight	80	53	22	94
Skin rash	65	81	36	93
Generalised lymphadenopathy	35	93	44	90
Oral ulcers	40	82	27	89
Oral candidiasis	45	90	43	91
Wasting	40	87	33	90
Maternal serology	100	87	59	100

The proposed Nairobi diagnostic criteria correctly classified 16/20 cases of AIDS and 97/123 cases without AIDS resulting in a sensitivity of 80 % and specificity of 79%. Using these criteria there were 26 false positive and four false negative results. By comparison the WHO criteria correctly diagnosed 12/20 cases of AIDS (sensitivity = 60%) and 115/123 cases without AIDS (specificity=94%) with eight false positive and eight false negative cases.

DISCUSSION

In this study two clinical criterias were evaluated. The WHO case definition for AIDS was fulfilled by 14% (20/143) of the children studied compared to 29.4% (42/143) who satisfied the Nairobi diagnostic criteria. The sensitivity of the WHO criteria in our study was 60% and is comparable to values seen in other studies. This low sensitivity has been improved upon by our proposed Nairobi diagnostic criteria which had a sensitivity of 80%, the highest recorded in any clinical criteria for definition of AIDS in children in Africa.

The improved sensitivity of the proposed criteria could be due to the fact that oropharyngeal candidiasis one of the main opportunistic manifestation of AIDS in Africa was included as a major diagnostic criteria. Another possible reason for the higher sensitivity of NDC compared to WHO criteria could be attributed to the inclusion of neurological involvement as a major diagnostic criteria in the proposed NDC. Neurological problems are common in HIV-1 infected children. Neuro-developmental delays in infants and neuropsychologic deficits in older children have been documented in 75 - 90% of children with HIV infection(14,15). In our study, delayed milestone and abnormal behaviour were significantly associated with AIDS. Seizures as a manifestation of HIV encephalopathy is a rare presentation and in this study convulsions was not significantly associated with AIDS. Clinical features that were found significantly associated with AIDS in our study were similar to other studies in Africa. Children with AIDS were more likely to have wasting, oral ulcers and candidiasis, pruritic dermatitis and generalised lymphadenopathy. As in other studies chronicity of symptoms such as cough, fever and diarrhoea were more likely to be associated with AIDS.

In this study, blood transfusion, the use of unsterilised instruments to break the skin, re-use of contaminated needles and sexual abuse of the child were not identified as being important risk factors for HIV-1 infection. The issue of sexual abuse was difficult to assess in a population where affected children are predominantly infants below 24 months of age as in this study and where discussion about sex itself is almost a taboo. We attribute the low specificity of both criteria evaluated to the fact that the clinical features of AIDS also occur in children with chronic illnesses that are common causes of paediatric admissions in Africa, such as pulmonary tuberculosis and protein energy malnutrition.

Ideal clinical criteria for paediatric AIDS would have both a high sensitivity and specificity. Unfortunately this is not often an achievable goal for many diagnostic tests, requiring that a trade off be made between sensitivity and specificity. This will depend on the purpose of the screening and the consequences of false positive and false negative tests. In the clinical setting it is important to have a highly sensitive test that will identify as many children with AIDS as possible since they will often require more intensive treatment than other children. The proposed Nairobi criteria are therefore better for this purpose than previous clinical

criteria. The fact that the NDC has a lower specificity and positive predictive value than previous clinical criteria is an inherent weakness. However, positive predictive value tends to increase with increasing prevalence. It is therefore reasonable to anticipate an increase in positive predictive value with the projected increase of children admitted to hospital with HIV/AIDS.

In this series, only four children were diagnosed as having AIDS beyond 36 months. Seventy five per cent of those with AIDS were below 24 months. This is consistent with the fact that most children who acquire HIV-1 infection perinatally are symptomatic by the second year of life. The early identification of these children is important in providing opportunities for improving their care and quality of life. Our study has highlighted the limitations of using clinical criteria alone for the diagnosis of AIDS in children. The development of a simple inexpensive test for diagnosis of HIV/AIDS in children below the age of 18 months therefore remains an urgent need.

Appendix 1

WHO clinical case definition for paediatric AIDS

Major signs

1. Weight loss or abnormally slow growth
2. Chronic diarrhoea >1 month
3. Prolonged fever >1 month

Minor signs

1. Generalised lymphadenopathy
2. Oro-pharyngeal candidiasis
3. Repeated common infections for example (otitis media pharyngitis, etc)
4. Persistent cough
5. Generalised dermatitis
6. Confirmed maternal HIV infection.

Diagnosis of AIDS is made if a child has at least two major signs and two minor signs in the absence of known causes of immunosuppression.

Appendix 2

Components of the proposed Nairobi Diagnostic Criteria.

(A) *Major findings*

1. Failure to thrive (FTT)
2. Persistent oropharyngeal candidiasis >4/52
3. Kaposis sarcoma
4. Neurological involvement (Bizarre neurological signs including unexplained delayed milestones, regression of milestones, and deterioration of psychomotor functions).
5. Recurrent severe bacterial and severe viral infections.

(B) *Minor findings*

1. Persistent fever for more than one month
2. Generalised lymphadenopathy
3. Generalised dermatitis
4. Persistent or intermittent diarrhoea
5. Chronic suppurative otitis media

(C) *Associated risk factors*

1. Maternal HIV infection
2. History of having received blood products and/or blood transfusion
3. Sexual abuse
4. Child prostitutes and street children
5. Re-use and use of non sterile equipment for piercing/ breaking the skin.

Interpretation

A diagnosis of AIDS is made if one has:

1. One major sign, three minor signs plus or minus one risk factor
2. Two major signs and at least one minor sign
3. One major sign, two minor signs and at least one or two risk factors.

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