DETERMINANT FACTORS OF LOW COGNITIVE, MOTORIC AND LANGUAGE PERFORMANCE OF HIV-INFECTED CHILDREN

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ABSTRACT

The effects of HIV infection on children's physical growth, psychological health, and neurodevelopment are essential. This study aims to know the determinants factor of low cognitive, motoric, and language performance of HIV-infected children. This study examined 68 HIV-infected children ranged 0 to 36 months selected by simple random sampling. The sample size was determined by sample calculation for cohort design. Cognitive, motoric, and language were assessed using the Cognitive Adaptive Test (CAT) and Clinical Linguistic and Auditory Milestone Scale (CLAMS) score, which are components of the Capute Scale. Data were analyzed using a cross tab, and a significant Pearson chi-square ($p < 0.05$) was used to identify the determinant factors. The result showed that CD4 level, length of antiretroviral treatment, age, stage of HIV infection, socioeconomic status, and family income were determinant factors of low cognitive, motoric, and language performance of HIV-infected children. The performance of cognitive, motoric, and language aspects in HIV children was affected by CD4 level, length of antiretroviral treatment, age, stage of HIV infection, socioeconomic status, and family income. Early intervention in developmental status is needed to prevent HIV-infected children's low cognitive, motoric, and language performance.

Keywords: children; cognitive; HIV; language; motoric

INTRODUCTION

Children with HIV infection are at risk of developmental and behavioral challenges 1. At the end of 2020, 2.1 million children were living with HIV/AIDS. Two million of them are located in sub-Saharan Africa.[1] Transmission vertically by the mother is the most route of infection of these children acquire HIV from HIV mothers during pregnancy, birth, or breastfeeding.[2] The early antiretroviral interventions reduce the risk of mother-to-child HIV transmission. However, the coverage of interventions is still not widely accessible or available in most low-middle-income countries where HIV incidence is high. On the other hand, 1 of 500 children gets new HIV infections per day. The increasing number of children receiving ART from 75,000 to 200,000 in 2020.[3]

The neurodevelopment aspects of HIV-children commonly affected were growth, gross motoric, social and personal performance, cognitive and language.[4] The main pathogenesis is virus entering the central nervous system (CNS) of foetal during pregnancy through transplacental transmission and mostly affecting microglial cells and oligodendrocytes, which results in neuronal injury in the developing brain.[5] This brain injury causes a significant encephalopathy in foetal. Most impairments affect cognitive, language, and motor functions.[6] The prevalence of these delays may be variated by almost 60%.[7] Delayed neurodevelopmental are particularly common in countries with limited treatment resources.[8] Clinical features include loss or failure to achieve appropriate developmental milestones, impaired brain growth, and global

or selective impairments in cognitive, language, motor, attention, behavior, and social skills that may affect day-to-day functioning.[10] Some degrees of cognitive decline may present even in the early and asymptomatic stages of HIV infection. The benefits of antiretroviral treatment for cognitive performance can be detected after only a few weeks of follow-up.[11,12]

The Capute Scales are screening tools that are widely used to assess neurodevelopmental delays, composed of CAT to assess cognitive function and CLAMS to evaluate language functions. This is an easy and practical screening neurodevelopmental assessment test for HIV-infected children in an outpatient setting.[13] With the ease of this test, we can cooperate it into routine practice and would be able to detect children with delayed development who will benefit from an early stimulation program early.[14] This study aimed to assess determinant factors that affected HIV-infected children's low motoric, cognitive, and language performance.[15]

We recruited 136 subjects as a sample base on the sample calculation of cohort design. The sample was divided into 68 HIV-infected groups and 68 healthy children as a control group.

MATERIAL AND METHODS

Samples that meet inclusion criteria were selected as subjects. The criteria for the HIV group were: confirmed diagnosis of HIV infection by serological test positive for HIV antibody and followed the treatment of an antiretroviral minimum of six months. Inclusion criteria for the healthy control group were negative for the antibody anti-HIV test. Exclusion criteria were another comorbid disease such as cerebral palsy and serious complications of HIV that caused the subject difficulty in following the assessment.

The HIV sample was recruited in pediatric policlinic Sanglah hospital, and a healthy control group was recruited in Taman Kanak-Kanak Werdi Kumara, Sanglah Hospital, Denpasar

The Capute Scales were used to examine the subject's cognitive, motoric, and language performance. The CLAMS consisted of 43 language items, and CAT consisted of 57 visuomotor, nonverbal problem-solving items.[16] In The first step, we determine the chronological age based on age. Then we assess the developmental quotient of each CAT and CLAMS by fulfilling questionnaires based on the subject's ability to pass the task. The Scores of Cat and Clams were categorized as delay under 70, suspect as 70-84, and normal as 85-120.[17] Data was analyzed using a cross tab, and a significant Pearson chi-square ($p < 0.05$) was used to identify the determinant factors.

RESULT

A total of 68 HIV-infected children were recruited as research subjects. Several factors affected Cat/Clasm score as a mirror of cognitive, motoric, and language performance. Table 1 explains the factors analyzed by multinominal regression to obtain factors that affect the values of Cat and Clams that have been categorized as suspect 70-84 and normal as 85-120. No delay category was found in the subject because of a history of antiretroviral treatment prior to examination. The Cat / Clams scores were examined at the first meeting and then after six months of observation. The first variable analyzed was gender, both male and female there were no differences in the value of Cat / Clams both in the initial month or the sixth month, evidenced by a p value> 0.05, which was not significant. The next variable is CD4 + levels. Most subjects with low Cat and Clams values are subjects with CD4 levels less than 25 cells / mm3, as evidenced by p 0.006 in the first month and p 0.003 in the sixth month. The next variable is the length of ARV administration, in which 89.3% -100% of subjects with low Cat and Clams values have ARV duration of fewer than 12 months. Based on age classification, age 25-36 months have a lower Cat value compared to other age groups, with a value of p 0.008 in the first month and p 0.01 in the sixth month.

Table 1. Analyses of Determinant Factors of Cat/Clams Score

Variable	First Examination						6-month Examination					
	CAT		p	CLAMS		p	CAT		p	CLAMS		p
	70-84	85-120		70-84	85-120		70-84	85-120		70-84	85-120	
Gender												
Male	12 (32.4)	25 (67.6)		12 (32.4)	25 (67.6)		14 (37.8)	23 (62.2)		12 (32.4)	25 (67.6)	
Female	15 (48.4)	16 (51.6)	0.218	14 (45.2)	17 (54.8)	0.205	16 (51.6)	15 (48.4)	0.329	14 (45.2)	17 (54.8)	0.324
CD4 Level												
<25 cells/mm3	11 (73.3)	4 (26.7)		10 (66.7)	5 (33.3)		12 (80.0)	3 (20.0)		10 (66.7)	5 (33.3)	
>25 cells/mm3	16 (30.2)	37 (69.8)	0.006	16 (30.2)	37 (69.8)	0.16	18 (34.0)	35 (66.0)	0.003	16 (30.2)	37 (69.8)	0.016
Length of ARV treatment												
< 12 months	27 (96.4)	1 (3.6)		25 (89.3)	3 (10.7)		28 (100)	0 (0)		25 (89.3)	3 (10.7)	
>12 months	0 (0)	40 (100)	0.000	1 (2.5)	39 (97.5)	0.000	2 (5.0)	38 (95)	0.000	1 (2.5)	39 (97.5)	0.000
Age Classification												
0-12 months	3 (21.4)	11(78.6)		4 (28.6)	10 (71.4)		4 (28.6)	10 (71.4)		4 (28.6)	10 (71.4)	
13-24 months	9 (29.0)	22 (71.0)	0.008	9 (29.0)	22 (71.0)	0.085	10 (32.3)	21 (67.7)	0.01	9 (29)	22 (71.0)	0.085
25-36 months	15 (65.2)	8 (34.8)		13 (56.5)	10 (43.5)		16 (69.6)	7 (30.4)		13 (56.5)	10 (43.5)	
Stage of HIV infection												
Asymptomatic	6 (15.4)	33 (84.6)		7 (17.9)	32 (82.1)		8 (20.5)	31 (79.5)		7 (17.9)	32 (82.1)	
Mild	9 (64.3)	5 (35.7)		8 (57.1)	6 (42.9)	0.001	9 (64.3)	5 (35.7)		8 (57.1)	6 (42.9)	
Moderate	10 (76.9)	3 (23.1)	0.000	9 (69.2)	4 (30.8)		11 (84.6)	2 (15.4)	0.000	9 (69.2)	4 (30.8)	0.001
Severe	2 (100)	0 (0)		2 (100)	0 (0)		2 (100)	0 (0)		2 (100)	0 (0)	
Nutritional status												
Good	11 (31.4)	24 (68.6)		11 (31.4)	24 968.6)		12 (34.3)	23 (65.7)		11 (31.4)	24 (68.6)	
Undernourish	15 (50.0)	15 (50.0)		14 (46.7)	16 (53.3)		17 (56.7)	13 (43.3)		14 (46.7)	16 (53.3)	
Malnourish	1 (33.3)	2 (66.7)	0.304	1 (33.3)	2 (66.7)	0.445	1(33.3)	2 (66.7)	0.180	1 (33.3)	2 (66.7)	0.445
Socio-economic status												
Low	17 (68.0)	8 (32.0)		16 (64.0)	9 (36.0)		19 (76.0)	6 (24.0)		16 (64.0)	9 (36.0)	
Middle	10 (25.6)	29 (74.4)		10 (25.6)	29 (74.4)		11 (28.2)	28 (71.8)		10 (25.6)	29 (74.4)	
High	0 (0)	4 (100)	0.001	0 (0)	4 (100)	0.002	0 (0)	4 (100)	0.000	0 (0)	4 (100)	0.002
Maternal Education												
Elementary school	1 (100)	0 (0)		1 (100)	0 (0)		1 (100)	0 (0)		1 (100)	0 (0)	
Junior high scholl	9 (45)	11 (55)		8 (40)	12 (60)		9 (45)	11 (55)		8 (40)	12 (60)	
Senior high scholl	14 (34.1)	27 (65.9)		14 (34.1)	27 (65.9)		17 (41.5)	24 (58.5)		14 (31.4)	27 (65.9)	
Bachelor degree	3 (50)	3 (50.0)	0.467	3 (50)	3 (50)	0.516	3 (50)	3 (50)	0.688	3 (50)	3 (50)	0.516
Father educational level												
Elementary school	3 (100)	0 (0)		3 (100)	0 (0)		3 (100)	0 (0)		3 (100)	0 (0)	
Junior high scholl	9 (42.9)	12 (57.1)		8 (38.1)	13 (61.9)		9 (42.9)	12 (57.1)		8 (38.1)	13 (61.9)	
Senior high scholl	13 932.5)	27 (67.5)		13 (32.5)	27 (67.5)		16 (40)	24 (60.0)		13 (32.5)	27 (67.5)	
Bachelor degree	2 (50)	2 (50)	0.128	2 (50)	2 (50)	0.131	2 (50)	2 (50)	0.246	2 (50)	2 (50)	0.131
Family income												
< 1 milion IDR	2 (7.1)	26 (92.9)		3 (10.7)	25 (89.3)		4 (14.3)	24 (85.7)		3 (10.7)	25 (89.3)	
1-2.5 milion IDR	20 (62.5)	12 (37.5)		18 (56.2)	14 (43.8)		20 (62.5)	12 (37.5)		18 (56.2)	14 (43.8)	
2.5-5 milion IDR	5 (62.5)	3 (37.5)	0.000	5 (62.5)	3 (37.5)	0.000	6 (75.0)	2 (25.0)	0.000	5 (62.5)	3 (37.5)	0.000

The stage of HIV infection was also analyzed, and it found that 100% of subjects with a severe stage had a low Cat / Clams value, followed by a moderate stage of 69.2% - 84.6%. Poor nutritional status at most has a low Cat / Clams value compared to good nutritional status, but the result is insignificant (p> 0.05. Low economic literacy mostly has low Cat / Clams values, which is significant with p <0.05. mothers with an education level only completed primary school as much as 100% had children with low Cat / Clams grades. Still, these results were not different from subjects with higher maternal education, evidenced by p> 0.05. This result is also similar to the father's education variable,

which is not statistically different from the value of CAT / CLAMS in subjects with fathers with low or high education. Furthermore, the last but not least is an analysis of family income, where children with a parent's income below 1 million rupiahs have a higher Cat / Clams value. In comparison, > 1 million rupiahs have a lower CAT / CLAMS value, and this is statistically significant (p= 0,000).

DISCUSSION

This study found that children with CD4 counts of less than 25 cells/mm3 had a lower difference in Cat/Clams scores than children who had CD4 levels of more than 25 cells/mm3. The results of this study are in accordance with research by Widyadharma et al., 2017 which stated that subjects with CD4 cells less than 200 cells/mm3 had lower cognitive function than subjects with CD4 levels of more than 200 cells/mm3.[18] Another study by Supadma et al., 2020 also stated that there was a relationship between CD4 levels and Capute Scale values in HIV-infected children compared to children who were not infected with HIV.[19]

Research by Ravindran et al., 2014 found that children with HIV tend to suffer cognitive deficits in the domains of attention, language, verbal learning and memory, visuomotor functions, fine motor performance, and executive functions.[17, 20]

Research by Cohen et al., 2015, stated that the cognitive performance of HIV-infected children is poor compared with healthy controls.[21,22] Gaining insight into these cognitive deficits is essential, as subtle impairments may progress to more pronounced complications that will influence future intellectual performance, job opportunities, and community participation of HIV-infected children.[23,24]

Research by Kandehwal et al., 2020 on malnourished children stated that the results indicated that children with SAM exhibit developmental delay across all domains.[22] Identifying multiple modifiable risk factors for developmental delay in children with Severe Acute Malnutrition will help devise early interventional strategies in low-middle income countries. This study found that most HIV-infected children were undernourished, although it was not statistically significant.[24] This can result from a series of chronic inflammation caused by HIV infection, which requires the HIV-infected child's body to undergo a higher metabolism to break down ATP to fight the virus. It is coupled with the release of inflammatory mediators, which also exacerbate carbohydrate, fat, and protein metabolism so that children lose a lot of energy and protein.[25] This loss of energy and protein, of course, inhibits nerve conduction which plays an important role in the intelligence process.[26]

According to Ruel et al., 2011, motor and cognitive deficits were significantly found in HIV-infected ART-naive Ugandan children with CD4 cell counts of 350 cells/lL and percentages of .15%. Early initiation of ART could prevent or reverse such deficits. In accordance with the results of this study which states that the length of ARV treatment has a significant effect on the value of Cat/Clams, the earlier a child is treated with ARV, the better his neuropsycomotor, cognitive, and language development will be. These results are also supported by Blokhuis et al., 2016 who stated that ART effectively reduces brain injury by intervening viral load and consequent inflammation.[24] Uninfected children from HIV mothers suffered a higher developmental delay than unexposed children in receptive and expressive language.[25]

Other research by Sania et al., 2019 stated that nursing patterns, parental education, stimulating factor, and environmental and nutritional factors contribute to child development. In contrast to this study's results, the family's socioeconomic status greatly affects the cognitive, motor, and language functions of children with HIV. The level of education of mothers and fathers in this study did not significantly affect cognitive, motor, and language functions.[26]

CONCLUSION

The CD4 level, length of antiretroviral treatment, age, stage of HIV infection, socioeconomic status, and family income were determinant factors of low cognitive, motoric, and language performance of HIV-infected children. It can be concluded that internal and external factors affect cognitive, motoric, and language. Further research must be conducted to assess how this factor affects HIV-infected children's cognitive, motoric, and language performance.

REFERENCES

1. Sherr. L, Natasha Croome, Katherine Parra Castaneda, Katie Bradshaw, Rocio Herrero Romero, 2014. Developmental challenges in HIV infected children—An updated systematic review. Children and Youth Services Review. 2016; 45:74–89
2. World Health Organization. 2020. Pediatric HIV and treatment of children living with HIVhttps://www.who.int
3. Andrade ASA, Deutsch R, Celano SA, Duarte NA, Marcotte TA, Umlauf A. Relationships among neurocognitive status, medication adherence measured by pharmacy refill records, and virologic suppression in HIV-infected patients. Journal Acquired Immune Deficiency Syndrome. 2012;62:282-92.
4. Mwaba SOC, Ngoma MS, Kusanthan T and Menon JA. The Effect of HIV on Developmental Milestones in Children. Journal of AIDS & Clinical Research. 2016; 6:1-6
5. McHenry MS, McAteer CI, Oyungu E. Neurodevelopment in Young Children Born to HIV-Infected Mothers: A Meta-analysis. Pediatrics. 2018; 141: 1-8
6. Bello AI, Jonathan NA Quartey, and Louisa A Appiah. Screening for developmental delay among children attending a rural community welfare clinic in Ghana. BMC Pediatrics 2013, 13:119 -125.
7. Kube D David A., William M. Wilson, MA, Mario C. Petersen, and Frederick B. Palmer CAT/CLAMS: Its Use in Detecting Early Childhood Cognitive Impairment Pediatric Neurology. 2018; 23(3): 208-215
8. Whitehead N, Potterton J, Coovadia A. The Neurodevelopment of HIV-infected Infants on HAART compared to HIV-exposed but uninfected infants. AIDS Care. 2014;26:497-504.
9. Nakasuja N, Allebeck P, Agren H, Musisi S, Katabira E. Cognitive dysfunction among HIV positive and HIV negative patients with psychosis in Uganda. PLoS One. 2012;7:1-5
10. Bunyasi E K, David John Coetzee. Relationship between socioeconomic status and HIV infection: findings from a survey in the Free State and Western Cape Provinces of South Africa. BMJ Open. 2017;7:1-5
11. Ngoma MS, Hunter JA, Harper JA. Cognitive and language outcomes in HIV-uninfected infants exposed to combined antiretroviral therapy in utero and through extended breastfeeding. AIDS. 2014; 28 (Suppl 3):S323–S330
12. Violari A, Mark F. Cotton, Louise Kuhn, Diana B. Schramm. 2019. A child with perinatal HIV infection and long-term sustained virological control following antiretroviral treatment cessation. Nature Communications. 2019;10:412-420
13. Weber V, Daniel Radeloff, Bianca Reimersa, Emilia Salzmann-Manrique, Peter Bader, MD, P. Neurocognitive development in HIV-positive children is correlated with plasma viral loads in early childhood. Medicine. 2017; 96:23-30.
14. Redmond SM, Tzy-Jyun Yao,2 Jonathan S. Russell Longitudinal Evaluation of Language Impairment in Youth With Perinatally Acquired Human Immunodeficiency Virus (HIV) and Youth With Perinatal HIV Exposure. Journal of the Pediatric Infectious Diseases Society, 2016;5 (Suppl 1): S33–S40,
15. Walker S.Y., Pierre R.B., Christie C.D.C., Chang S.M. Neurocognitive function in HIV-positive children in a

developing country. International Journal of Infectious Diseases. 2013; 17:e862-e867.
16. Rice ML, Buchanan AL, Sibery GK, Malee KM, Zeldow B, Frederick T. Language impairment in children perinatally infected with HIV compared to child who were HIV-exposed and uninfected. Journal Dev Behaviour Paediatric. 2012;33:112-23.
17. Ravindran OS, Mrudula P. Rani1, G. Priya. 2014. Cognitive Deficits in HIV Infected Children. Indian Journal of Psychological Medicine. 2014;36(3):255-259
18. Widyadharma E, Satiti S, Nuradyo D, Setyopranoto A,Wijayanti. The Difference of CD4 Count Between HIV Positive Patients With Cognitive Decline and Without Cognitive Decline. Biomedical & Pharmacology Journal. 2017; 10(2), 969-978.
19. Supadma N, Budiapsari, PI, Wati KDK, Artana IWD. Correlation of Capute Scores with CD4 Count among Human Immunodeficiency Virus-infected Children in Sanglah Hospital, Bali, Indonesia. Open Access Macedonian Journal of Medical Sciences. 2020;8:45-48.
20. Ranjitkar S, Hysing M, Kvestad I, Shrestha M, Ulak M, Shilpakar JS, Sintakala R, Chandyo RK, Shrestha L and Strand TA. Determinants of Cognitive Development in the Early Life of Children in Bhaktapur, Nepal. Front. Psychol. 2019; 10:2739.- 2745
21. Cohen S, Jacqueline A. ter Stege, Gert J. Geurtsen, Henriette J. Scherpbier, Taco W. Kuijpers, Peter Reiss, Ben Schmand, and Dasja Pajkrt. Poorer Cognitive Performance in Perinatally HIV-Infected Children Versus Healthy Socioeconomically Matched Controls. HIV/AIDS. Clinical Infectious Diseases. 2015; 60(7):1111–1119
22. Khandelwal N, Mandliya J, Nigam K, Patil V, Mathur A, Pathak A. Determinants of motor, language, cognitive, and global developmental delay in children with complicated severe acute malnutrition at the time of discharge: An observational study from Central India. PLoS ONE. 2020; 15(6): 1-7
23. Ruel TD, Michael J. Boivin, Hannah E. Boal, Paul Bangirana, Edwin Charlebois, Diane V. Havlir, Philip J. Rosenthal, Grant Dorsey, Jane Achan, Carolyne Akello, Moses R. Kamya, and Wong JK. Neurocognitive and Motor Deficits in HIV-Infected Ugandan Children With High CD4 Cell Counts. Clinical Infectious Diseases 2012;54(7):1001–1009
24. Blokhuis C, Neeltje A Kootstra, Matthan wA Caan, Dasja Pajkrt. Neurodevelopmental delay in pediatric HIV/AIDS: current perspectives. Neurobehavioral HIV Medicine. 2016;7 1–13
25. Wedderburn CJ, Shunmay Yeung, Andrea M Rehman, Jacob A M Stadler, Raymond T Nhapi, Whitney Barnett, Landon Myer, Diana M Gibb, Heather J Zar, Dan J Stein, Kirsten A Donald. Neurodevelopment of HIV-exposed uninfected children in South Africa: outcomes from an observational birth cohort study. Lancet Child Adolesc Health. 2019; 3: 803–813
26. Sania A, Sudfeld CR, Danaei G, Fink G, McCoy DC, Zhu Z, Fawzi MCS, Akman M, Arifeen SE, Barros AJD, Bellinger D, Black MM, Bogale A, Braun JM, van den Broek N, Carrara V, Duazo P, Duggan C, Fernald LCH, Gladstone M, Hamadani J, Handal AJ, Harlow S, Hidrobo M, Kuzawa C, Kvestad I, Locks L, Manji K, Masanja H, Matijasevich A, McDonald C, McGready R, Rizvi A, Santos D, Santos L, Save D, Shapiro R, Stoecker B, Strand TA, Taneja S, Tellez-Rojo MM, Tofail F, Yousafzai AK, Ezzati M, Fawzi W. Early life risk factors of motor, cognitive and language development: a pooled analysis of studies from low/middle-income countries. BMJ Open 2019;9:1-6