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Factors associated with anxiety in children and adolescents with HIV infection

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Abstract

Introduction: Children and adolescents with human immunodeficiency virus (HIV) infection, usually have several complex problems, both biological and psychiatric. This study aimed to investigate factors associated with anxiety in children and adolescents with HIV.

Material and methods: This cross-sectional study was conducted at allergy-immunology outpatient clinic in Sanglah Hospital, Denpasar, Indonesia. A total of 60 children and adolescents aged 7-18 years were assessed using Spence children's anxiety scale to detect anxiety. Associated factors included age, gender, orphan status, primary caregiver, clinical stage, CD4+ count, hospitalization, and disclosure status. Statistical analysis was performed using χ^2 test, followed by multivariate analysis with binary logistic regression. *P*-value less than 0.05 was considered significant.

Results: Elevated anxiety symptoms were found in 22 subjects (36.7%) in the form of separation anxiety symptoms (72.7%), obsessive-compulsive disorder (50.0%), physical injury fear (45.5%), panic-agoraphobia (36.3%), social phobia (27.2%), and generalized anxiety disorder (22.7%). In multivariate analysis, older age (PR: 6.91; 95% CI: 1.55-30.89%) and orphan status (PR: 9.56; 95% CI: 1.12-81.89%) were independently associated with elevated anxiety symptoms.

Conclusions: Elevated anxiety symptoms were prevalent among HIV-infected children and adolescents, primarily in the form of separation anxiety. Older age and orphan status were independently associated with elevated anxiety symptoms.

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Key words: anxiety, HIV, children, associated factors.

Introduction

Efforts to prevent vertical transmission of human immunodeficiency virus (HIV) in the last 15 years have significantly decreased HIV mortality rate. The Joint United Nations Programme on HIV and acquired immunodeficiency syndrome (AIDS) reported that new HIV infections among children have declined by 52%, from 310,000 in 2010 to 150,000 in 2019 [1]. Antiretroviral treatment has also increased the number of children with HIV/AIDS surviving to adolescence [2]. Children with HIV infection not only have biological problems, but are also at greater risk of psychiatric and mental disorders [3]. The prevalence and risk of mental and psychiatric disorders in children and adolescents with HIV/AIDS ranged from 24.3% to 61.0% [4, 5]. Anxiety has been reported to be the most prevalent psychiatric disorder, which includes social phobia, agoraphobia, generalized

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anxiety disorder, panic disorder, obsessive-compulsive disorder, and specific phobias [4]. Betancourt *et al.* [6] showed that children with HIV-positive status were 1.77 times more likely to suffer from an anxiety disorder. However, Gadow *et al.* [7] did not find a significant difference in mental disorder prevalence between children aged 6-18 years with perinatal HIV infection and in non-infected children. The discrepancy in findings warrants a replication of the study in different settings.

Multiple factors have been reported to be associated with emotional and psychiatric disorders in children and adolescents with HIV infection, including older age [4, 8], female gender [4, 9], no school attendance [8], no sport participation [8], violence [8], knowledge of own HIV status [9], and caregiver HIV status [8]. An undetectable viral load had a protective effect, decreasing the risk of behavioral problems with an odds ratio of 0.4. Even though viral load had a protective effect, CD4+ level was not associated with anxiety [4].

Anxiety in children and adolescents with HIV worsens their condition, leading to a negative impact on behavior, low medication compliance, school and learning challenges, poor self-care, low social function [10], and the requirement of increased attention and awareness. Early detection of mental disorders is essential component of comprehensive care, as anxiety is easy to identify, and several screening tools are available and simple to apply. One of these tools is Spence children's anxiety scale (SCAS) developed by Spence in 1998. SCAS has a sensitivity of 49.09%, specificity of 95.92%, positive predictive value of 93.10%, and negative predictive value of 62.67% in detecting various anxiety symptoms [11]. It has been translated into many languages, and adapted to various cultures with good reliability and validity [12]. SCAS has been translated into Bahasa Indonesia and is available on official website. SCAS also has been routinely used to screen anxiety in children and adolescents in Sanglah Hospital.

Although anxiety has been reported to be the most prevalent mental problem in children with HIV infection, there are limited reports particularly addressing factors associated with anxiety symptoms. Therefore, the objective of this study was to assess anxiety symptoms and associated factors in children and adolescents with HIV infection.

Material and methods

This study was an analytic cross-sectional study, conducted at allergy-immunology outpatient clinic in Sanglah Hospital, Bali, Indonesia, in December 2020, until the sample size was fulfilled. This study included children and adolescents between 7 and 18 years of age with HIV infection. Diagnosis of HIV was established based on clinical manifestations, and virology or serology evaluation. Exclusion criterion was refusal to participate in this study.

Sample size was calculated to assess two-tailed hypothesis and association between two variables with un-paired categorical data, with an assumption of error alpha of 5% and power of 80%. Minimum required sample was determined to be 22 subjects in each anxiety and non-anxiety groups.

Variables included subject characteristics, such as age, gender, education, caregiver, orphanhood, height, weight, nutritional status, disclosure, CD4+ count, clinical stage of HIV infection, antiretroviral therapy, and elevated anxiety.

Anxiety was determined based on elevated anxiety symptoms, identified as a SCAS T-score of above 60. T-score is a standardized score calculated from total distribution of SCAS scores within community sample based on gender and age. There are six sub-dimensions of SCAS, consisting of generalized anxiety, panic attack and agoraphobia, separation anxiety, fear of physical injury, social phobia, and obsessive-compulsive disorder. SCAS score was divided into two categories, such as elevated anxiety symptoms and normal [12]. Patient age was determined at the time of interview, age was expressed in years as all subjects were more than 12 months old, and partial years were rounded to the nearest year. Subject gender was determined by phenotype and categorized into male and female. Educational status was defined by level of education the patient had reached when the research was conducted and grouped into categories of no education, primary, secondary, and tertiary [13]. Primary caregivers were people responsible for giving and fulfilling patient's daily needs, such as parents, grandparents, and other caregivers which further divided into parent(s) or non-parental [13]. Orphan status was determined in subjects by divided them into both parents alive, both parents died, and one parent died, which further divided into both parent alive and one or both parents died [13]. Subject's height was measured in a full standing position without footwear and expressed in centimeters (cm). Subject's weight was measured by a scale in standing position and expressed in kilograms (kg). Nutritional status was measured based on actual participant's weight compared to ideal body weight (based on the World Health Organization [WHO] curve) by Waterlow. This variable was divided into sub-categories of obese (more than 120%), overweight (110-120%), well-nourished (90-110%), mild malnutrition (80-90%), moderate malnutrition (70-80%), and severe malnutrition (below 70%) [14]. CD4+ count was determined based on patient's most recent CD4+ laboratory examination, and was subsequently divided into two categories, such as immune-suppressed and non-immune-suppressed. Cut-off value was 350 cells/mm^3 based on WHO recommendation of initiation of highly active antiretroviral therapy, in which patients with CD4+ above 350 cells/mm^3 were considered non-immune-suppressed and patients with CD4+ below 350 cells/mm^3 were considered immune-suppressed [15]. Clinical stage was determined based on the WHO clinical staging for infants and children with proven HIV/AIDS infection, consisting stages I-IV, which further divided into stage I-II and III-IV [16]. Hospitalization frequency was defined as the number of hospitalizations prior to the recruitment, which further divided into ever hospitalized versus never hospitalized. Disclosure of HIV status was measured by asking parents/caregivers if the child know his/her HIV status [17]. Disclosure of HIV status including non-disclosed, partially disclosed, and fully disclosed, which further categorized into disclosed and non-disclosed [18].

Parents/caregivers of participants aged older than seven years old with proven HIV infection were given information regarding the study during clinic visit. All parents/caregivers who agreed to enroll their children in the study, provided written informed consent. Study data were obtained during hospital visits using three modalities of data collection, including interview with caregiver, SCAS form, and medical records. Interview with caregiver was performed to collect basic characteristic, such as identity of subjects, age, gender, educational status, primary caregiver, and vital status of parents (alive or dead). At the time of interview, nutritional status was determined with measurement of weight and height of participants. Age at diagnosis, duration of hospital care, recent CD4+ count, and clinical stage at the time of interview were derived from medical record. A single team member of the study delivered the interview, measurements, and data collected from medical records. SCAS questionnaires were given to all participants of the study, and were completed by circling appropriate responses by themself. When the subject could not comprehend the question enough, then an independent physician accompanied the filling process, gave any explanation when needed, without any attempt to influence the response.

Characteristics of subjects were presented descriptively by a table and narrative, including age, gender, educational status, caregiver, condition of parents, weight, height, nutritional status, duration of hospital care, recent CD4+ count, clinical stage, parental HIV status, and anxiety score. Categorical variables, both nominal and ordinal, were presented as absolute number and percentage. Numerical variables were given as mean and standard deviation when the data were normally distributed, and as median and interquartile range when the data were not normally distributed. Chi-square test was used to evaluate association between factors and anxiety in children with HIV. Prevalence ratio (PR) was used to determine association value, which indicated level of anxiety risk in children and adolescents with HIV, with a 95% confidence interval (CI). Multivariate logistic regression analysis was performed to obtain adjusted prevalence ratio for factors associated with elevated anxiety symptoms. A value of $p < 0.05$ was considered significant.

This study was approved by the Research Ethics Committee at Udayana University Medical School, Sanglah Denpasar Hospital with number 2463/UN.14.2.2.VII.14/LT/2020, and signed informed consents were obtained from all parents/caregivers.

Results

During the period of the study, 60 HIV-positive children and adolescents, whose ages ranged from 7 to 18 years were enrolled in this study. Thirty-one (51.7%) subjects were males, and the median age of the participants at the initiation of the study was 11.5 years (range, 9-13 years). The median age at diagnosis was 3 years (range, 1-5 years) and the mean duration of hospital care was 8.32 ± 2.89 years. Detailed subject characteristics are illustrated in Table 1.

Elevated anxiety symptoms were identified in 22 (36.7%) subjects. Of the participants with anxiety symptoms, the majority had separation anxiety symptoms (72.7%), followed by obsessive-compulsive disorder (50.0%), physical injury fear (45.5%), panic-agoraphobia (36.3%), social phobia (27.2%), and generalized anxiety disorder (22.7%) (Table 2).

Chi-test showed a significant association between elevated anxiety symptoms in children and adolescents with HIV and age (PR: 3.40; 95% CI: 1.44-8.03%; $p = 0.001$), orphan status (PR: 2.13; 95% CI: 1.06-4.32%; $p = 0.027$), HIV clinical stage (PR: 2.44; 95% CI: 1.38-4.31%; $p = 0.014$), current CD4+ count (PR: 2.08; 95% CI: 1.12-3.85%; $p = 0.030$), and hospitalization frequency (PR: 2.18; 95% CI: 1.06-4.80%; $p = 0.036$). Gender, primary caregiver, and disclosure status were not associated with elevated anxiety symptoms (Table 3). Binary logistic regression test showed that individuals aged 12 years old or above, and those who had one or more parent who died, were more likely to have anxiety symptoms, with PR: 6.91; 95% CI: 1.55-30.89%; $p = 0.011$ and PR: 9.56; 95% CI: 1.12-81.89%; $p = 0.039$, respectively (Table 4).

Discussion

Anxiety disorders included social phobia, separation anxiety, agoraphobia, generalized anxiety disorder, panic disorder, obsessive-com- pulsive disorder, and specific phobias. We found that 36.7% of all study subjects experienced elevated anxiety symptoms, with a majority of the patients experiencing separation anxiety (72.7%). Mellins *et al.* [4] reported that the most prevalent non-substance psychiatric disorders among perinatally HIV-infected youth were anxiety disorders, accounting for 46% of the total sample. Similarly, Scharko [5] and Woollet *et al.* [9] found almost the same prevalence rates of anxiety among HIV-infected children (24.3% and 25.0%, respectively). In contrast, a study by Kinyanda *et al.* [19] reported a much lower prevalence rate of anxiety among perinatally HIV-infected children and adolescents (only 9.0%), though the study similarly found that the most prevalent anxiety disorder was separation anxiety (4.6%).

Widespread use of highly active antiretroviral therapy has allowed children with perinatal HIV infection to reach adolescence and young adulthood in large numbers [20]. Older adolescents infected with HIV were at higher risk of suffering from many behavioral challenges. This study found that the patients above 12 years of age were significantly associated with elevated anxiety symptoms. Furthermore, multivariate analysis showed that age above 12 years old was independently associated with elevated anxiety level (PR: 6.91; 95% CI: 1.54-30.89%). This finding was supported by Mellins *et al.* [4], who showed that older youth (range, 13-16 years old) were 2.01 times more likely to have behavioral disorders than younger children (95% CI: 1.12-3.31%). Kinyanda *et al.* [19] also reported that adolescents (age group, 12-17 years old) were at higher risk for developing emotional disorders compared to children (age group, 5-11 years old), with an adjusted OR = 2.66 (95% CI: 1.89-3.74%). This was an expected finding from a cognitive development

Table 1. Baseline characteristics of the participants, *N* = 60

Variable	*n* (%)
Age (year)	
7-12	30 (50.0)
13-18	30 (50.0)
Gender	
Male	31 (51.7)
Female	29 (48.3)
Patient's education	
No education	0 (0.0)
Primary	43 (71.7)
Secondary	14 (23.3)
Tertiary	3 (5.0)
Nutritional status	
Well-nourished	40 (66.7)
Mild malnutrition	11 (18.3)
Moderate malnutrition	4 (6.7)
Severe malnutrition	1 (1.7)
Overweight	4 (6.7)
Orphanage status	
Both parents alive	33 (55.0)
Both parents died	18 (30.0)
One of the parents died	9 (15.0)
Duration of hospital care, years	
Mean, SD	8.32 (2.89)
Age at diagnosis, years (range)	
Median, IQR	3.00 (1–5)
HIV clinical stage	
I-II	52 (86.7)
III-IV	8 (13.3)
Current CD4+ count	
Mean, SD, cell/mm^3	731.4 (408.0)
ARV therapy	
First-line	39 (65.0)
Second-line	21 (35.0)
Hospitalization frequency	
None	27 (45.0)
Once	22 (36.7)
More than once	11 (18.3)
Disclosure of HIV status	
Non-disclosed	45 (75.0)
Partially disclosed	14 (93.3)
Fully disclosed	1 (6.7)
Primary caregiver	
Parents	40 (66.7)
Grandparents	9 (15.0)
Others	11 (18.3)
Area of living	
Rural	33 (55.0)
Urban	27 (45.0)

point of view, as 12- to 16-year-old children develop abstract thinking and logical reasoning, and can understand psychological complications that may arise from life-long HIV infection [13]. Also, in older children and adolescents, receiving the diagnosis of HIV/AIDS may lead to psycho-social difficulties, including fears about the future, feelings of guilt or shame, and estrangement from peers or neighbors, which may in turn hinder their school performance [21]. Therefore, special awareness and assessment of anxiety in this age group are fundamental.

Our study showed that orphan status contributed to a higher risk of anxiety in children and adolescents with HIV infection, and multivariate analysis determined that this variable was independently associated with elevated anxiety symptoms (PR: 9.56; 95% CI: 1.11-81.89%). Atwine *et al.* [21] reported similar findings that orphan children had significantly more psychological problems, including anxiety, depression, anger, and disruptive behavior. This study also reported that orphan status could increase the risk of anxiety 6.4 times (range, 3.4-12.1 times) compared to non-orphaned children. Cluver *et al.* [22] showed that AIDS-orphaned children had higher anxiety scores compared to non-orphaned children ($p < 0.001$; mean = 5.59 and mean non-orphaned = 5.08). In this study, the researcher also reported that after four years, AIDS-orphaned children had even higher anxiety scores compared to non-orphaned children. Bankole *et al.* [13] found that depression was much more common in children and adolescents with HIV infection who were orphans (69.6%) than non-orphans (5.9%). The experience of loss and bereavement is generally difficult for all children, though older children may feel more grief due to loss of a parent. Unlike adults, younger children often do not feel the full impact of loss, as they may not immediately understand the finality of death. This lack of understanding prevents them from going

Table 2. Anxiety symptoms diagnosis in the study, *N* = 60

Variable	*n* (%)
Elevated anxiety symptoms	22 (36.7)
Separation anxiety	16 (72.7)
Obsessive-compulsive disorder	11 (50.0)
Physical injury fear	10 (45.4)
Panic agoraphobia	8 (36.3)
Social phobia	6 (27.2)
Generalized anxiety disorder	5 (22.7)
Non-elevated anxiety symptoms	38 (63.3)

Table 3. Variables associated with HIV infection with elevated anxiety symptoms*

Variable	Elevated anxiety symptoms *n* = 22	Non-elevated anxiety symptoms *n* = 38	PR	*p*-value	95% CI
Age (year), *n* (%)					
13-18	17 (56.7)	13 (43.3)	3.400	0.001	1.44-8.03%
7-12‡	5 (16.7)	25 (83.3)			
Gender, *n* (%)					
Female	10 (34.5)	19 (65.5)	0.891	0.734	0.46-1.74%
Male‡	12 (38.7)	19 (61.3)			
Orphan status, *n* (%)					
One or both parents died	14 (51.9)	13 (48.1)	2.139	0.027	1.06-4.32%
Both parents alive‡	8 (24.2)	25 (75.8)			
Primary caregiver, *n* (%)					
Non parental	11 (50.0)	11 (50.0)	1.727	0.103	0.90-3.31%
Parent(s)‡	11 (28.9)	27 (71.1)			
HIV clinical stage, *n* (%)					
III-IV	6 (75.0)	2 (25.0)	2.438	0.014	1.38-4.32%
I-II‡	16 (30.8)	36 (69.2)			
Current CD4+ count, *n* (%)					
< 350	9 (60.0)	6 (40.0)	2.077	0.030	1.12-3.85%
≥ 350‡	13 (28.9)	32 (71.1)			
Hospitalization frequency, *n* (%)					
Ever hospitalized	16 (48.5)	17 (51.5)	2.182	0.036	1.06-4.80%
Never hospitalized‡	6 (22.2)	21 (77.8)			
Disclosure HIV status of children, *n* (%)					
Disclosed	6 (40.0)	9 (60.0)	1.125	0.757	0.54-2.34%
Non-disclosed‡	16 (35.6)	29 (64.4)			

χ^2 test; ‡ – reference

Table 4. Multivariate analysis of factors associated with elevated anxiety symptoms

Variable	PR	*p*-value	95% CI
Age more than 12 years old	6.91	0.011	1.55-30.89%*
One or two parents died	9.56	0.039	1.12-81.89%*
Primary caregiver non-parental	4.27	0.196	0.47-38.67%
HIV clinical stage III-IV	2.95	0.334	0.33-26.46%
Current CD4+ count < 350 cells/mm^3	4.77	0.750	0.85-26.68%
One or more hospitalization	2.19	0.248	0.58-8.28%

Significant p < 0.05

through the grief process, which is necessary for recovery. In addition, children's mourning behavior tends to fluctuate, making it difficult for adoptive parents and teachers to recognize symptoms and to provide appropriate support. Therefore, this puts children at risk of growing up with unresolved negative emotions and without sufficient recovery from grief for months or years following the loss of their parent(s) [13, 22].

Although HIV clinical stage, current CD4+ count, and hospitalization frequency were associated with elevated anxiety symptoms as shown in bivariate analysis, these variables were not significantly associated in multivariate analysis. This may be due to interaction between variables, such as HIV clinical stage, CD4+ count, and hospitalization frequency, that finally cause the same effect as anxiety. For instance,

children with low CD4+ count would have severe immunosuppression and a higher risk of disease progression, resulting in more frequent hospital admission. The multivariate analysis also showed that confidence interval of older age and orphanhood variable become wider than in bivariate analysis, and this was presumably due to the association between age and orphanhood to other variables. A study of Mokgatle and Madiba [23] reported that orphan children were more likely to be older, being diagnosed late, and delayed starting ART as well as a high possibility of infection in children before being diagnosed with HIV infection and subsequent increased risk of hospitalization.

This study have several limitations. First, the SCAS is a scale to assess anxiety symptoms and as such, the results regarding anxiety should be interpreted as a screening only. Moreover, this study only assessed anxiety on one occasion, so it could not show a temporal relationship between these factors and elevated anxiety symptoms. This study also did not explore the social support structure from extended family that is common in Indonesia and may impact psychological problems. The duration of orphanhood, and whether it was the mother or father who died, were also not evaluated, which might impact younger children in specific ways due to dependency and bonding associated with parenthood. This study did not elaborate on the reason for primary caregiver not disclosing HIV status, which warrants further investigation. Finally, the sample size was small, and the results had wide confidence intervals; however, the subjects represented our overall HIV outpatient clinic patients, allowing the relatively small sample size to represent the population.

Further larger studies would be required to determine the specificity and sensitivity of SCAS as a diagnostic measure of anxiety in children and adolescents with HIV infection in Indonesia. Also, larger sample sizes would obtainmore precise results and reveal other risk factors associated with anxiety in children and adolescents with HIV infection.

Despite its' limitations, the high proportion of anxiety identified in this study expand knowledge related to anxiety symptom screenings for children and adolescents with HIV infection. Further diagnostic process when anxiety levels are elevated were warranted to enable assessment by psychiatrist or social pediatrics.

The results of this study also contribute to the better management of children and adolescents with HIV infection. Identification of subpopulation with concomitant mental health problem will enable various intervention techniques to be appropriately addressed as an adjunct therapy in children and adolescent with HIV infection.

Conclusions

This study found that elevated anxiety symptoms were prevalent among children and adolescents with HIV infection. Elevated anxiety symptoms were independently associated with children over the age of 12 and children who are orphans. Screening for anxiety symptoms followed by early intervention is necessary for children and adolescents living with HIV to lessen negative long-term consequences.

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Conflict of interest

The authors declare no conflict of interest.

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