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Prevalence of Electrocardiogram Abnormalities in Human Immunodeficiency Virus-Infected Children

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Abstract: HIV is an important cause of childhood morbidity and mortality affecting more than 1.3 million children worldwide, one of the morbidity is cardiac abnormalities. Cardiovascular abnormalities are still subclinical during childhood then become symtomatic in adulthood. Electrocardiography is effective to detect cardiac diseases. This study aimed to assess ECG changes in HIV infected children and describe ECG abnormalities in HIV-infected children with or without HAART. From 70 subjects, we found the most common abnormality was sinus tachycardia in 17 patients (24.3%), sinus bradycardia 1 patient (1.4%) and 2 patients with sinus arrhythmia (2.9%). The mean QTc interval was 0.42 seconds (±0.07) and 14 patients (20%) had prolongation. The mean PR interval was 0.12 seconds (±0.02), 11 patients (15.7%) experienced prolongation of PR interval. The mean QRS duration was 0.06 seconds (±0.09). Left ventricular enlargement was present in 6 patients (8.6%), conduction disturbance which is characterized by Bundle branch block was found in 2 patients (2.9%) and ST changes was seen in 2 patients (2.9%). Other ECG abnormalities are characterized by right ventricle hyperthropy in 4 patients and a patient had T tall. The prevalence of cardiac abnormalities based on ECG examination from this study was 51.3%, consist of heart rhythm abnormality, prolonged PR interval, prolonged QTc interval, bundle branch block, ventricle hypertrophy and ST changes.

Keywords: Electrocardiography, HIV, HAART, Children

1. Introduction

HIV is an important cause of childhood morbidity and mortality affecting more than 1.3 million children worldwide [1]. In 2011, around 33-36 million people live with HIV and about 0,8% is aged 15-49 years old [2]. Vertically acquired HIV infection is a devastating disease in childhood which may affect many organs, including cardiovascular system [3]. Cardiac involvement may have diverse manifestations from initial asymptomatic presentation to overt heart failure and sudden death [4]. Cardiac abnormalities were directly responsible for death in 11.8% young children and the incidence increased up to 25% in children older than 10 years old [5].

Cardiac involvement may either be due to direct infection of cardiac myocytes or due to various opportunistic infections [6]. The exact pathogenesis of cardiac manifestations remains unclear but most likely is multifactorial. It may be due to prolong immune suppression, opportunistic infections, viral infections, autoimmune response, drug related cardiotoxicity and nutritional deficiencies [7].

Cardiovascular abnormalities in childhood still subclinical and become symptomatic in adulthood. This abnormality can be related to premature myocardial infarction (MI) or stroke, pericardial effusion, lymphocytic interstitial myocarditis, LV (left ventricular) diastolic dysfunction, dilated cardiomyopathy (frequent myocarditis), infective endocarditis and malignancy (sarcoma Kaposi muscle heart,

immunoblastic cell lymphoma B) [8, 9].

Electrocardiographic (ECG) and echocardiography abnormalities had been demonstrated in HIV-positive patients. The ECG abnormalities documented include arrhythmias, low-voltage QRS, non-specific ST-segment, T-wave changes, poor R-wave progression, right bundle branch block, axis deviations, enlargement of various heart chambers and QTc prolongation. The manifestations of HIV infection in organs other than the heart mask the clinical evidence of cardiac disease in these subjects. Electrocardiography is effectively used to detect cardiac diseases. Cardiac diseases in HIV infection are important concern in public health because they are usually undetected, but increasing mortality rates [10].

The effects of ARV therapy and its interactions are related to cardiovascular system directly through abnormality of lipids and protease inhibitors (PIs) and increased of serum statin concentrations. Provision of this therapy may alter repolarization and prolong the QT interval, thereby increasing the risk of sudden death. The long-term effect of HAART on cardiovascular system is better understood in adults HIV, whom present the side effects of cumulative antiretroviral exposure [11]. Therefore, we aimed to study of the ECG abnormalities in HIV-infected children. The aim of the study is to assess ECG changes in HIV infected children and describe the ECG abnormalities in HIV-infected children with or without HAART.

2. Materials and Method

This study was a cross sectional study, conducted at Cardiology and Allergy-Immunology Division/Department of Child Health, Medical Faculty of Udayana University/Sanglah Hospital Denpasar, by taking the ECG data of children with HIV from Cardiology database-Sanglah since Desember 2016 until January 2018. Target population was inpatient and outpatient children with HIV infection in Sanglah Hospital.

Inclusion criteria are HIV infected children who were on HAART, age under 18 years old, complete ECG data. The exclusion criteria were children whom on medications with cardiovascular effects (such as anti arrhythmic drugs, theophylin and adriamycin) and children with pre-existing cardiac diseases. Sample size calculation using the formula based on categoric descriptive with minimum sample size was 47.

HIV infected patient is patient with diagnosis of HIV infection during hospital visit, serologically diagnosed, recorded in the medical record and have received HAART regularly who has good compliance. Gender is determined by phenotype male or female.

Age is chronological age of the subjects stated in years, if age > 6 months, rounded up and if < 6 months, rounded down. The clinical stage of HIV was based on WHO 2014 criteria. Clinical stages was categorized as 1 through 4 (see appendix), acording to the current clinical stage.

Highly active antiretroviral therapy (HAART) was defined as any regimen including 3 or more antiretroviral drugs from 2 or more antiretroviral drug classes (nucleoside reverse transcriptase inhibitor (NRTIs), non-nucleoside reverse transcriptase inhibitor (NNRTIs) and protease inhibitor (PIs).

CD4+ is a glycoprotein found on the surface of immune cells such as T helper cells, monocytes, macrophages and dendritic cells, including the absolute and percentage CD4 lymphocytes count. The absolute CD4 count is a measurement of how many functional CD4 is circulating in blood and reported as the number of CD4 cells per cubic millimeter of blood. The CD4 percentage (CD4%) represents the percentage of total lymphocytes that are CD4 cells.

The CD4 data from within 3 months of subjects' electrocardiography examination was obtained. The children under 5 years of age use CD4%, while children over 5 years of age using absolute CD4.

QTc interval prolongation is the prolongation of QT interval after corrected heart rate which can be evaluated through ECG examination. It would be said prolongation if the interval value of QTc > 0.44 second.

The prolonged of PR interval is the extension of the PR interval evaluated by an ECG examination. It said to be prolonged if the value of the PR interval exceeds the limit value according to age and heart rate.

Data was analyzed statistically by SPSS 22. All results are reported as the percentage of patients found to have the given abnormality or as the mean±1 standard deviation. This study was approved by the Research Ethics Committee at Udayana University Medical School, Sanglah Hospital, Denpasar.

3. Results

There were 70 subjects in this research with age range from 0 to 14 years old, the median age was 6.5 years. About 64.3% subjects are stage one. The CD4 level devided into percentage and absolute. Median of CD4 absolute was 417 and mean of CD4 percentage 21.25%. Fifty five patients were in HAART (78,6%) and the rest about 15 patients (21.4%) were not in HAART. The subjects' characteristics were shown in table 1.

Table 1. *Subjects characteristic.*

Clinical characteristics	n=70
Age, median (SD)	6.5 (2.98)
< 5 years old, n (%)	23 (32.9)
> 5 years old, n (%)	47 (67.1)
Gender, n (%)	
Male	46 (65.7)
Female	24 (34.3)
Current stage of HIV, n (%)	
Stage I	45 (64.3)
Stage II	6 (8.6)
Stage III	8 (11.4)
Stage IV	11 (15.7)
CD4+ absolute, median (min-max)	417 (2-12967)
CD4+ percent, mean (SD)	21.25 (17.6)
HAART, n (%)	
Yes	55 (78.6)
No	15 (21.4)

The ECG data is assessment including rhythm, PR interval, QRS duration, QTc interval, bundle branch block, left ventricle hypertrophy and ST changes. Overall, as many as 36 patients (51.4%) had ECG abnormalities including heart rythme, prolonged PR interval, prolonged QTc interval, bundle branch block, ventricle hypertrophy and ST changes, while the rest 34 patients (48.6%) had normal ECG pattern. The most common abnormality was sinus tachycardia in17 patients (24.3%). There were 50 patients (71.4%) with sinus rhythm, the remaining had respectively sinus bradycardia 1 patient (1.4%) and 2 patients with sinus arrhythmia (2.9%). The mean QTc interval was 0.42 seconds (±0.07) and 14 patients (20%) experienced prolongation. The mean of PR interval was 0.12 seconds (±0.02). Eleven patients (15.7%) experienced prolongation of PR interval. The mean QRS duration was 0.06 seconds (±0.09). Left ventricular enlargement was found in 6 patients (8.6%), conduction disturbance characterized by Bundle branch block was present in 2 patients (2.9%) and ST change were seen in 2 patients (2.9%). Other ECG abnormalities were characterized by right ventricle hypertrophy in 4 patients, and one patient had a T tall. Complete ECG characteristics was presented in Table 2.

Table 2. *Electrocardiograph characteristic.*

ECG characteristic	n=70
Normal sinus rhythm, n (%)	50 (71.4)
Sinus tachycardia	17 (24.3)
Sinus bradycardia	1 (1.4)
Arrhythmia	2 (2.9)
PR interval, mean (SD)	0.12 (0.02)
Prolonged PR interval, yes, n (%)	11 (15.7)
QRS duration, mean (SD)	0.06 (0.09)
QTc interval, mean (SD)	0.42 (0.07)
Prolonged QTc interval, yes, n (%)	14 (20)
Bundle branch block, yes, n (%)	2 (2.9)
Left ventricle hypertrophy, yes, n (%)	6 (8.6)
ST changes, yes, n (%)	2 (2.9)
Right ventricle hypertrophy, yes, n (%)	4 (5.7)
Others, yes, n (%)	1 (1.4)

From all subjects, we got 36 patients and 34 patients with and without ECG abnormalities respectively, we described their characteristics based on CD4 level, HIV stage and HAART. The comparison of both groups were presented in Table 3.

Table 3. *Comparison between patients with and without ECG abnormalities.*

Characteristic	ECG abnormalities	
	Yes (34)	No (36)
CD4 percentage, mean (SD)	34 (20.56)	33 (41.8)
CD4 absolute, median (min-max)	279 (2.19-12967)	435 (2-1518)
HIV Stadium n (%)		
Stadium I	20 (44.4%)	25 (55.6%)
Stadium II	3 (50%)	3 (50%)
Stadium III	6 (75%)	2 (25%)
Stadium IV	7 (63.6%)	4 (36.4%)
HAART		
Yes	24 (43.65)	31 (56.4%)
No	12 (80%)	3 (20%)

From all patients with ECG abnormalities, we compared patients whom with or without antiretroviral therapy. The comparison of both groups on ECG abnormalities was presented in Table 4.

Table 4. *Comparison of ECG abnormalities in patient with and without HAART.*

ECG abnormalities	HAART	
	Yes (55)	No (15)
Sinus tachycardia, yes, n (%)	8 (47.1)	9 (52.9)
Sinus bradycardia, yes, n (%)	1 (100)	0 (0)
Arrhythmia, yes, n (%)	2 (100)	0 (0)
Prolonged QTc interval, yes, n (%)	8 (57.1)	6 (42.9)
Prolonged PR interval, yes, n (%)	9 (81.8)	2 (18.2)
Bundle branch block, yes, n (%)	2 (100)	0 (0)
Left ventricle hypertrophy, yes, n (%)	4 (66.7)	2 (33.3)
ST changes, yes, n (%)	1 (50)	1 (50)
Right ventricle hypertrophy, yes, n (%)	2 (50)	2 (50)
Others, yes, n (%)	0 (0)	1 (100)

Sinus tachycardia was found more in patients with HAART than in patients who had not used HAART, but the sinus bradycardia and arrythmia were found in patient with HAART. The number of patients experienced QTc interval prolongation equal in patients with or without HAART. We noted that patients with HAART experience more PR interval than patients without HAART, 9 patients and 2 patients respectively. More patients with HAART experienced bundle branch block and left ventricle hypertrophy. Meanwhile the numbers of ST changes and right ventricle hypertrophy, are proportional in patients with and without HAART.

4. Discussion

HIV infection and AIDS are known can impact heart and causing its sequele. Cardiac manifestations of HIV and AIDS have become important causes of morbidity and mortality [12]. Some studies about cardiac involvement in children with HIV based on echo and ECG finding have been published. The ECG can identify heart abnormalities in HIV/AIDS patients to detect whether they were suspected of having cardiac disease [13].

The prevalence of heart abnormalities detected by ECG among HIV positive children in this study was 51.4%, which was higher than that previously reported by Lobega et al (26.5%) [14]. Sinus tachycardia, prolonged QTc and prolonged PR interval were the three most common ECG abnormalities found in this study.

The ECG assess normal sinus rhythm and variation of beat interval which may reflect the current state of autonomic, respiratory and neurohumoral systems [15]. In this study we found sinus tachycardia in 17 patients (24.3%), which might be due to current febrile illness, anemia, myocarditis and increased metabolic demand in HIV patients. These conditions induce autonomic dysfunction and increased sympathetic activity [13]. Arrhythmia is uncommon in both children and adults with HIV infection. The arrhythmia commonly found usually benign, including sinus tachycardia, first degree heart block, junctional escape rhythm and

premature atrial beat. These arrhythmias rarely progress to supraventricular or ventricular tachycardia, second-degree heart block, right bundle branch block and prolonged QTc, which have high mortality rates [16].

Several HIV protease inhibitors (PIs) including atazanavir, ritonavir, lopinavir and saquinavir are risky to cause impairement of atrioventricular conduction velocity as proven by prolonged PR interval. Prolongation of PR and QRS intervals can be caused by sodium channel blockage and the slowing conduction velocity in atrioventricular and His-Purkinje conduction systems as well as in cardiomyocytes [11]. PR interval is influenced by autonomic nervous system and depend on long-lasting voltage-gated calcium channel conductance. Higher plasma concentrations of PIs are associated with inhibition of CYP3A by ritonavir or that the combination effects of ritonavir and other PIs which lead to inhibition of calcium (PR) and sodium (PR and QRS) conductance while intraventricular bundle branch blocks can also resulted from an intrinsic impairment of conduction due to disease stages or aging [17].

A longer PR interval may indicate increased predisposition to first-degree AV block and is associated with 20–30% increased risk of atrial fibrillation [18, 19], despite controversies regarding its prognostic significance in healthy general population [18, 20]. In our study, from 55 patients treated with HAART, 8 patients was using second line HAART including PI. Nine patients whom was given HAART experienced prolonged PR interval and two of them were using second line HAART.

QT interval prolongation is an irregularity of the electrical activity in heart which is risky for ventricular arrhythmias. The prevalence of QT prolongation is reported higher among hospitalized HIV patients. This is possibly due to their medications or acquired form of long QT syndrome (LQTS) which arised from HIV infection. Among those medications that are currently used in HIV patients, antibacterial, antifungal, psychotropic drugs and antihistamines have been associated with QT prolongation or torsades de pointes (TdP), a life-threatening ventricular arrhythmia. Pentamidine, trimethoprim-sulfamethoxazole, ciprofloxacin and clarithromycin are several medications used in HIV infection to treat opportunistic infections that could induce QT prolongation. Drug-induced QT prolongation has been shown that the HIV protease inhibitors (lopinavir, nelfinavir, ritonavir and saquinavir) can cause dose dependent block of human ether-a`-go-go– related gene (HERG) channels, suggesting that protease inhibitors could predispose individual to QT prolongation and TdP. Efavirenz, a novel non nucleoside reverse transcriptase inhibitor, was also reported to cause QT prolongation and severe ventricular arrhythmia [12].

Several studies showed QTc interval prolongation across the age spectrum and had the greatest correspondence with CD4 cell counts below 200 cells/ml and chronic exposure to anti retroviral therapy. In a recent study, QTc prolongation was reported in 18% of perinatal-infected Nigerian children compared to 0% children in an HIV-negative control group. It is unclear whether QTc interval prolongation reflects increasing HIV-disease severity within these children because no relationship was found with disease classification, nor was CD4 cell count or time of infection formally compared with QTc interval length [21]. In this study, none of the patients was on any HAART which could induce QTc prolongation, although some of them are still in cotrimoxazole therapy, so it could not be explained by drugs. It might be due to hypocalcemia, hypokalemia or an unrecognized pathway, autonomic dysfunction or through myocardial ischemia or cardiomyopathies due to HIV infection.

Ventricle hypertrophy seen on ECG, was found both equal in patient with and without HAART. The exact mechanisms of this adverse effects on ventricle mass in HIV-positive are thought to be related to mitochondrial toxicity. Many studies have shown that HIV virions directly affect myocardial cells and are associated with local release of cytokines and other factors leading to inflammation, myocarditis and dilated cardiomyopathy. In addition, the increament or decreament of ventricle mass has been suggested to be associated with opportunistic infections, malnutrition and HAART [13].

5. Conclusion

HIV may be complicated by cardiovascular abnormality in children. The prevalence of cardiac abnormalities based on ECG examination from this study was 51.3%, consist of heart rhythm abnormality, prolonged PR interval, prolonged QTc interval, bundle branch block, ventricle hypertrophy and ST changes.

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References

[1] S. Lubega, G. W. Zirembuzi, P. Lwabi. Heart disease among children with HIV/AIDS attending the paediatric infectious disease clinic at Mulago Hospital. African health sciences. 2005; 5 (3): 219-26.

[2] UNAIDS. 2012 Report on the Global AIDS epidemic. http://www.unaids.org.

[3] A. Sims, C. Hadigan. Cardiovascular complications in children with HIV infection. Curr HIV/AIDS Rep. 2011; 8: 209-14.

[4] N. S. Idris, D. E. Grobbee, D. Burgner, *et al*. Cardiovascular manifestations of HIV infection in children. Eur J Prev Cardiol. 2015; 22: 1452-61.

[5] S. E. Lipshultz, K. A. Easley, E. J. Orav, S. Kaplan, T. J. Starc, et al. Cardiac dysfunction and mortality in HIV-infected children: the prospective P2C2HIV multicentre study: pediatric pulmonary and cardiovascular complications of vertically transmitted human immunodeficiency virus (P2C2 HIV) study group. Circulation. 2000; 102: 1542-8.

[6] C. Am, G. J. Nuovo. Histologic and in situ viral findings in the myocardium in cases of sudden, unexpected death. Mod Pathol. 2002; 15: 914-22.

[7] R. H. Merchant, M. M. Lala. Common clinical problems in children living with HIV/AIDS: systemic approach. Indian J Pediatr. 2012; 79: 1506–13.

[8] S. E. Lipshultz. Dilated cardiomyopathy in HIV-infected patients. N Engl J Med. 1998; 339 (16): 1153-5.

[9] W. G. Harmon, G. H. Dadlani, S. D. Fisher, S. E. Lipshultz. Myocardial and pericardial disease in HIV. Curr Treat Options Cardiovasc Med. 2002; 4 (6): 497-509.

[10] I. C. Okoye, E. N. Anyabolu. Electrocardiographic abnormalities in treatment-naïve HIV subjects in south-east Nigeria. Cardiovasc J Afr. 2017; 28: 1-5.

[11] N. Patel, S. Abdelsayed, M. Veve, C. D. Miller. Predictors of clinically significant drug-drug interactions among patients treated with nonnucleoside reverse transcriptase inhibitor-, protease inhibitor, and raltegravir-based antiretroviral regimens. Ann Pharmacother. 2011; 45 (3): 317.

[12] M. U. Sani, B. N. Okeahialam, Jos, Kano. QTc interval prolongation in patients with HIV and AIDS. J Natl Med Assoc. 2005; 97: 1657-1661.

[13] P. O. Njoku, E. C. Ejim, B. C. Anisiuba, S. O. Ike, B. J. C. Onwubere. Electrocardiographic findings in a cross-sectional study of human immunodeficiency virus (HIV) patients in Enugu, south-east Nigeria. Cardiovasc J Afr. 2016; 27: 252-257.

[14] I. C. Okoye, N. D. Anyabolu. Electrocardiographic abnormalities in treatment-naïve HIV subjects in south-east Nigeria. Cardiovasc J Afr. 2017; 28 (5): 315-318.

[15] R. C. McIntosh, J. D. Lobo, B. E. Hurwitz. Current assessment of heart rate variability and QTc interval length in HIV/AIDS. Curr Opin HIV AIDS. 2017; 12 (6): 528-533.

[16] S. Nalmas, R. Nagarakanti, J. Slim, E. Abter, E. Bishburg. Electrocardiographic changes in infectious diseases. Hospital Physician. 2007; 15-27.

[17] B. Charbit, E. Gayat, P. Voiriot, F. Boccara, P. M. Girard, C. Funck-Brentano. Effects of HIV Protease Inhibitors on cardiac conduction velocity in unselected hiv-infected patients. Clin Pharmacol Ther. 2011; 9: 1-7.

[18] N. S. Idris, M. M. H. Cheung, D. E. Grobbee, D. Burgner, N. Kurniati et al. Effects of paediatric HIV infection on electrical conduction of the heart. Open Heart. 2016; 3: 1-8.

[19] J. B. Nielsen, A. Pietersen, C. Graff, B. Lind, JJ Struijk et al. Risk of atrial fibrillation as a function of the electrocardiographic PR interval: results from the Copenhagen ECG Study. Heart Rhythm. 2013; 10: 1249-56.

[20] S. Cheng, M. J. Keyes, M. G. Larson, E. L. McCabe, C Newton-Cheh et al. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. JAMA. 2009; 301: 2571–7.

[21] O. Ige, S. Oguche, C. Yilgwan, H. Abdu, F. Bode-Thomas. The QT interval in human immunodeficiency virus-positive Nigerian children. J Med Trop. 2014; 16: 61.