Therapeutics, Pharmacology and Clinical Toxicology
Vol XIII, Number 3, September 2009
Pages 300-305

THERAPEUTICAL PRACTICE

ECHOCARDIOGRAPHIC ASPECTS IN HIV INFECTED/AIDS CHILDREN AND ADOLESCENTS

Ana Maria Tudor[1], Ioana Anca[2]

[1.] National Institute of Infectious Diseases "Matei Balş", University of Medicine and Pharmacy "Carol Davila" Bucharest
[2.] Institute for Mother and Child Care "Alfred Rusescu", University of Medicine and Pharmacy "Carol Davila" Bucharest

Abstract. Cardiac lesions are described in HIV infected patients, including children. The most characteristic anatomic aspect on echocardiography in HIV cardiomyopathy is dilated left ventricle. Cardiomyopathy correlates with low survival rate. We performed a retrospective study on 59 HIV infected children and adolescents to identify the echocardiographic changes associated with AIDS. Main cardiac lesions found were dilated cardiomyopathy and left ventricle hypertrophy. Cardiac involvement was more frequent in immunosuppressed patients.
Keywords: HIV, immunosuppression, cardiomyopathy, children, echocardiography

Introduction

Cardiac involvement in HIV infection was mentioned from the beginning of HIV epidemic when histology studies showed that the prevalence of myocardial abnormalities in HIV-positive patients ranged from 25% to 75% [1,2]

Data from the pre HAART era showed that 2% of all HIV infected patients will die because of cardiac complications [3]. Early studies conclude that HIV infected newborns have a higher risk to die if they have cardiac lesions at birth compared to those without cardiac involvement. 78% of the HIV infected newborns with severe left ventricle dysfunction and 29% with moderate left ventricle dysfunction died during first year of life compared to 8% death in HIV infected newborns with normal cardiac function and 0% newborn not HIV infected but with HIV infected mothers.[4].

Correlation of cardiomyopathy with immunosuppression and AIDS defining associated diseases is well documented in literature [5]. The most frequent association of cardiomyopathy was with HIV encephalopathy [6] Several studies showed that patients with encephalopathy have a higher risk to die of heart failure than HIV infected patients without encephalopathy.

Introduction of Highly Active Antiretroviral Therapy (HAART) transformed HIV infection into a manageable disease and increased patients' survival, but brought a new challenge: metabolic complication and cardiovascular risk as a long term adverse events of antiretroviral drugs. [7].

In this context it is clear that there are a large number of etiologic agents that can cause cardiac lesions in HIV infection. Etiologic agents, proven or possible cause of cardiac disease, associated with HIV infection range from HIV itself to opportunistic agents and from malignancies to antivirals, antibiotics and antifungal agents (table I)[4,8-16]

Even though the myocytes are not the primary target of HIV, they can be infected in early stages of the disease, starting the cardiac lesions associated with HIV infection. Another aspect that should be considered is that opportunistic infections and

Ana Maria Tudor
University of Medicine and Pharmacy "Carol Davila" Bucharest
email: terapeutica@terapeutica.ro

Agent		Clinical manifestations
Viruses	HIV	Myocarditis, dilated cardiomyopathy
	CMV	Myocarditis, pericarditis
	EBV	Cardiac failure
Bacteria	*M. tuberculosis*	Pericarditis
	M. avium complex	Pericarditis, Cardiac Failure
	S. pneumoniae	Pericarditis
	Staphylococcus aureus	Pericarditis
Fungi	*Candida spp.*	Endocarditis, Myocarditis, Pericarditis
	Cryptococcus neoformans,	Endocarditis, Myocarditis, Pericarditis
	Coccidioides immitis	Endocarditis, Myocarditis, Pericarditis
	Histoplasma capsulatum	Endocarditis, Myocarditis, Pericarditis
Protozoa	Toxoplasma Gondii	Myocarditis
Malignancies	Kaposi Sarcoma	Pericardial, Myocardial or Epicardial lesions
	Lymphomas	Pericardial, Myocardial lesions
Antiretrovirals	NRTI	Toxic Myocarditis
	IP	Myocardial Infarction
Antineoplastic drugs	Doxorubicin	Toxic Myocarditis
	Vincristine	Toxic Myocarditis
Antimicrobials	Cotrimoxazole	Arrhythmias
	Pentamidine	Arrhythmias
	Pyrimethamine	Arrhythmias
	Foscarnet	Arrhythmias
	Ganciclovir	Arrhythmias
	Amphotericin B	Arrhythmias

Table I. Biologic agents associated with cardiac lesions in HIV infection

neoplasms associated with AIDS and the drugs used to treat them can induce cardiac abnormalities as well.

The etiopathogenesis of atherosclerosis in treated HIV infected patients is complex and is not fully understood yet. It is clearly proven that most of the antiretroviral combinations used determine metabolic changes that pose a high cardiovascular risk on long term [13].

Echocardiography is the most sensitive and specific method in the evaluation of cardiomyopathy, although the gold standard for diagnosis is endomyocardial biopsy [17].

Taking these aspects into consideration we conducted an observational retrospective study regarding cardiac echographic aspects in 59 HIV infected children and adolescents admitted to the National Institute of Infectious Diseases, Bucharest between 01.01.2000 and 31.12.2004.

The aim of this study was to identify anatomic and functional cardiac aspects in children and adolescents with HIV/AIDS and to correlate them with CD4 levels and concomitant opportunistic infections.

Methods

Patients. We performed echocardiography in 59 HIV infected children and adolescents admitted for an acute problem or for a routine HIV evaluation, to the National Institute of Infectious Diseases Bucharest between 01.01.2000 and 31.12.2004. Mean age in studied patients was: 12.31 years. Sex distribution in studied patients was: male/female= 35/24. We used CDC revised classification for HIV staging and we found 4 patients in B1 stage, 12 in stage B2, 10 in stage B3, 14 in stage C2 and 19 in stage C3. There was no patient in stages A or C1.

Echocardiography We performed Doppler echocardiography at the Institute for Mother and Child Care "Alfred Rusescu" evaluating anatomic and functional indexes:

- anatomic: volumes and diameters for left and right ventricles
- functional: ejection fraction of left ventricle

We compared the cardiac indexes' values with the normal values for actual body surface and not for age since HIV infected children had body indexes (weight and height) below normal values. [18].

For cardiomyopathy diagnosis we used the clas-

sification of the European Society of Cardiology: "A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality." [19].

We used medical records to obtain data about immunosuppression level, opportunistic infections at the moment of cardiac assessment and patients' medical history, as well.

All patients underwent physical evaluation, including height, weight and body surface area calculation.

For statistical analysis we used Microsoft Excel with Analysis Tool Pack and EpiInfo 3.5.1 software.

Results

Out of 59 studied patients we identified 34 patients with different echocardiographic abnormalities associated with cardiomyopathy, 23 patients with normal cardiac parameters, two patients had pericarditis, one associated with systemic tuberculosis and another one with pneumococcal sepsis. The last two patients with pericarditis were excluded from statistical analysis since their condition was not associated with cardiomyopathy and the number of cases with pericarditis was too low for a valuable analysis.

The compared characteristics of the studied patients are summarized in table II.

The mean age in patients with cardiomyopathy was 12.8 years and, in those with normal echography, it was 11.6 years. Figure 1 shows the age distribution in the two studied groups and the mean trend. The differences in age distribution between the studied groups had no statistical significance.

Sex distribution was similar in both groups.

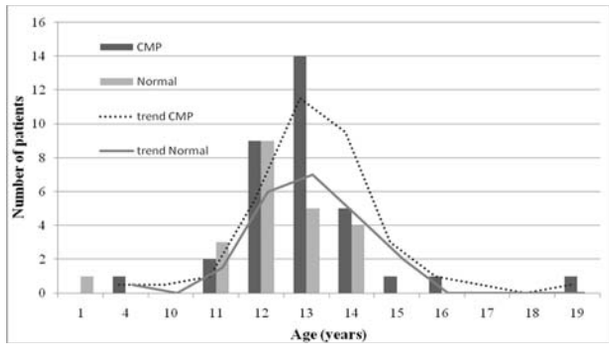

Figure 1. Age distribution and trend of means among studied patients

Male/female ratio was 1.4 in patients with abnormal echocardiography and 1.5 in the other group. There is no statistical significance in differences between sex distribution among the studied groups, p=0.9 (OR=0.92, CI95%: 0.27-3.09).

Given the fact that those two groups have similar distribution regarding age and sex, we used the group of children with normal echocardiography as comparison group in our statistical analysis.

The stage of HIV infection in both groups at the time of echocardiography is illustrated in figure **2**.

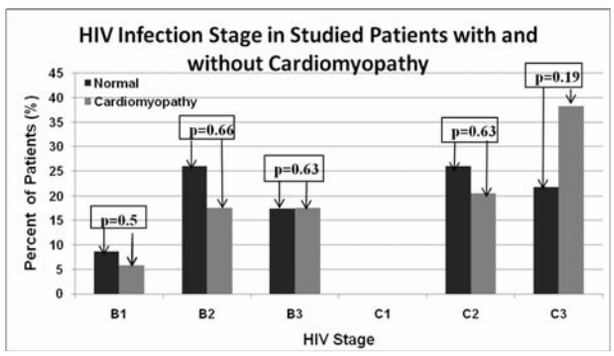

Figure 2. Stage of HIV Infection in Studied Patients with and without Cardiomyopathy (echocardiographic diagnosis)

Characteristics	Patients with Cardiomyopathy (N=34)				Patients with Normal echocardiography (N=23)			
	Mean	Standard deviation	Min	Max	Mean	Standard deviation	Min	Max
Age (years)	12.8	2.13	4	19	11.8	2.7	1	14
Weight (Kg)								
Height (cm)								
Body surface (m^2)	1.04	0.2	0.6	1.6	1.03	0.25	0.5	1.5
CD4 (cell/mm^3)	274	272	7	899	302	267	10	890

Table II. Characteristics of Studied Patients with and without Cardiomyopathy (Echocardiographic Diagnosis)

Opportunistic Diseases	Cardiomyopathy	Normal	P value
Tuberculosis	11	6	0.6
HIV encephalopathy	10	2	0.04
Recurrent pneumonia	19	9	0.9
Digestive Candidiasis	20	16	0.5
Wasting syndrome	3	2	0.6

Table III. Opportunistic Diseases associated to HIV/AIDS in studied patients

As figure 2 shows, most of the patients with cardiomyopathy have advanced HIV infection, respectively C stage, whereas most of the patients with normal echocardiography are in B stage. However, the differences between different stages in studied groups have no statistical significance.

The most frequent infection found in our study was recurrent pneumonia and candidiasis. The rate was similar among children with cardiomyopathy and with normal echocardiographic measurements. HIV encephalopathy was more frequent in patients with cardiomyopathy, statistically significant versus patients with normal echocardiography (p=0.04) (table III).

Figure 3. Echographic aspect in one studied patient

Anatomic indexes

Out of 34 patients with abnormal echocardiography, 14 patients had enlarged LV volume (figure 3), 8 had hypertrophic LV, and 2 had enlarged volume associated with hypertrophy of LV. Enlarged right ventricle volume was found in 5 children. In 5 cases, both ventricles were enlarged.

The image in figure 3 shows enlarged left ventricle volume in one studied patient at the end of systole and at the end of diastole. These two parameters define the dilated cardiomyopathy associated with HIV infection.

In patients with left ventricle hypertrophy we found no cases with arterial hypertension, or with anatomic or functional valvular lesions.

Functional indexes

14 children had low left ventricle (LV) ejection fraction, meaning 41% of the patients with cardiomyopathy had the ejection fraction below the normal limit of 49% [20]

The HIV infection stage in patients with dilated left ventricle was: C3- 9 cases, B3 - 5 cases, in patients with normal echocardiography there were 4 cases with B3 stage and 5 cases with C3 stage (table IV).

Immunosuppression level was measured by CD4 count in our study. In patients with impaired car-

Characteristics	Patients with Dilated Left Ventricle (N=20)	Patients with normal echocardiography (N=23)
Mean Age (years)	13	11.8
Mean Body surface (m^2)	1.06	1.03
Mean CD4 ($cell/mm^3$)	220	302
HIV stage (number of patients)		
B1	0	2
B2	4	6
B3	5	4
C1	0	0
C2	3	6
C3	9	5

Table IV. HIV infection stage in the studied patients with dilated left ventricle

diac parameters the mean CD4 level was 274cells/mm^3, while in patients with normal echocardiography the mean CD4 level was 304 cells/mm^3. In patients diagnosed with dilated left ventricle, the mean CD4 level was even lower, 220 cells/mm^3. (see tables II and IV).

Most of the patients with abnormal echocardiography 55.8% (19/34) had a CD4 level under 200 cells/mm^3, while 40% (9/23) had the same level of immunosuppression in patients with normal echocardiography. There is no statistical significance in the differences between patients with CD4 < 200 and CD4>200 regarding a dilated left ventricle versus patients with a normal left ventricle volume, p=0.519.

In our study, we did not find differences of statistical significance between patients with dilated left ventricle and those with normal echocardiography with respect to the C3 stage of HIV infection, p=0,13; OR=2,5 CI95% (0,75-8,5).

Discussions

Cardiomyopathy is an entity described in AIDS patients before HAART era. The clinical importance of cardiomyopathy associated with HIV is the correlation with severe prognosis.

Echocardiography is the most used diagnostic tool, since it is easy to perform, not invasive and does not necessitate sedation, a factor that could influence cardiac performances. [17].

Age is one of the most important factors that influence the echocardiographic parameters. In order to evaluate the influences on our results, we compared the mean age in patients with and without normal echocardiography. The difference between means is about 1.2 years – showing that younger children are at lower risk to develop cardiomyopathy, but this value has no statistical significance in our study.

Patients' gender has no impact on normal value ranges for cardiac assessment [18, 21] and its similar distribution in our studied groups excludes the gender bias in our study.

Most researchers agree that the most important factor in cardiomyopathy pathogenesis is the level of immunosuppression [6]. In our study most of the patients with cardiomyopathy 26/34 (76%) were in late stages of HIV infection B3, C2, C3, compared to 65% in studied patients with normal echocardiography, but the difference has no statistical significance (p=0.5).

The mean CD4 levels in our patients was 274 cells/mm^3 in the group with cardiomyopathy and 302 cells/mm^3, higher than the values that literature showed to be associated with cardiomyopathy 145 cells/mm^3 and respectively 210 cells/mm^3 in a cohort study on 416 infected adult patients in Rwanda [5]. This can explain why we did not find a strong correlation between low CD4 levels and cardiomyopathy in our study. The high CD4 levels found in our patients can be the result of HAART or a different duration of HIV infection between the patients we studied and those reported in literature. There is little literature data regarding cardiomyopathy in children.

In our study the most frequent cardiac lesion was dilated left ventricle 21/57 (36.8%), followed by hypertrophy of the left ventricle 8/57 (14%) and dilated right ventricle 5/57 (8.7%). This data is similar with other authors' reports, showing that dilated cardiomyopathy is the main cardiac abnormality in HIV infected patients. [6]

Association between cardiomyopathy and HIV encephalopathy in our study was similar to literature data [6], suggesting that cardiac involvement in the HIV infection appears in late stages and it is mainly caused by intense viral replication and immunodepression. Similar rates of recurrent pneumonia among the two studied groups underscore the fact that heart manifestation are not a sign of cor pulmonale, but more likely are a direct consequence of HIV infection.

Limitations

We performed a retrospective observational study which allowed us to identify some of the echocardiographic aspects in HIV infected children and adolescents. The main limitation in our study was the low number of patients which impacted on our statistical analysis. We did not assess the impact of antiretroviral treatment on studied patients.

Conclusions

Literature data on cardiomyopathy associated with HIV in children are scarce, that is why we consider that this echocardiographic assessment on 57 patients brought useful information in this area. In our study the most frequent finding was the dilated left ventricle as single lesion or associated with hypertrophic left ventricle or dilated right ventricle. As we suspected, most of the patients with cardiomyopathy were in late stages of HIV

infection and had low CD4 levels.

We consider that periodic echocardiography in HIV infected children is indicated, especially in those with immunosuppression with opportunistic infections that can mask discrete cardiac symptoms.

References

1. d'Amati G, di Gioia CR, Gallo P. Pathological findings of HIV-associated cardiovascular disease. *Ann N Y Acad Sci* **2001; 946:23–45.**

2. Lewis W. AIDS: cardiac findings from 115 autopsies. *Prog Cardiovasc Dis* **1989; 32:207–215.**

3. Tovo PA, de Marino M, Gambiano C et al. Prognostic factors and survival in children with perinatal HIV infection. *Lancet* **1992;339:1249-1253,** European Collaborative Study. Natural history of vertically acquired human immunodeficiency virus-1 infection. *Pediatrics* **1994;94:815 – 819,** Italian Register for HIV infection in Children. Features of perinatally infected with HIV-1 surviving longer than 5 years. *Lancet* **1994;343:191-195.**

4. Pizzo PA, Wilfert CM. *Pediatric AIDS. The challenge of HIV infection in Infants, Children and adolescents 3rd edition* **Lippincott, Williams and Wilkins, 1998; 21: 335-354.**

5. Twagirumukiza M, Nkeramihigo E, Seminega B, Gasakure E, Boccara F, Barbaro G. Prevalence of Dilated Cardiomyopathy in HIV-Infected African Patients Not Receiving HAART: A Multicenter, Observational, Prospective, Cohort Study in Rwanda. *Current HIV Research,* **2007; 5:129-137.**

6. Barbaro G. Pathogenesis of HIV-associated heart disease. *AIDS* **2003; 17 (suppl 1):S12–S20.**

7. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination Antiretroviral Therapy and the Risk of Myocardial Infarction. *N Engl J Med,* **2003; 349:1993-2003.**

8. Rene E, Rodriguez RE, Nasim S, Hsia Judith, Sandin RL, Ferreira Andrea, Hilliard Betty A, Ross AM and Garrett CT. Cardiac myocytes and dendritic cells harbor human immunodeficiency virus in infected patients with and without cardiac dysfunction: Detection by multiplex, nested, polymerase chain reaction in individually microdissected cells from right ventricular endomyocardial biopsy tissue. *The American Journal of Cardiology,* **Volume 68, Issue 15, 1 December 1991, Pages 1511-1520.**

9. Heidenreich PA, EisenbergMJ, Kee LL, et al. Pericardial effusion in AIDS. Incidence and survival. *Circulation* **1995; 92: 3229-3234.**

10. Epstain Barr -Luginguhl LM, Orav EJ, Mc Intosh K, Lipshultz SE. Cardiac morbidity and related mortality in children with HIV infection. *JAMA* **1993;269:2869 – 2875.**

11. Hofman P, Drici MD, Gibelin P, et al. Prevalence of toxoplasma myocarditis in patients with acquired immunodeficiency syndrome. *Br Heart J* **1993;189:894-901.**

12. Khan NU; Ahmed S; Wagner P; Rumley RL; Movahed A. Cardiac involvement in non-Hodgkin's lymphoma: with and without HIV infection. *Int J Cardiovasc Imaging.* **2004; 20(6):477-81.**

13. Grinspoon S, Carr A. Cardiovascular Risk and Body-Fat Abnormalities in HIV-Infected Adults. *N Engl J Med* **2005; 352:48-62.**

14. Barbaro G. Cardiovascular manifestations of HIV infection. *Circulation* **2002;106:1420-5**

15. Girard PM, Katlama Ch, Pialoux G. *VIH Edition* **2004, Doin Editeurs Groupe Liaisons SA ,Chapitre 36:425 -434.**

16. Rerkpattanapipat P, Wongpraparut N, Jacobs LE, Kotler MN. Cardiac manifestation of acquired immunodeficiency syndrome. *Arch Internn Med* **2000;160:602-608**

17. Khunnawat C, Mukerji S, Havlichek D, Touma R, Abela GS. Cardiovascular Manifestations in Human Immunodeficiency Virus-Infected Patients. *Am J Cardiol.* **2009 Jan 15; 103(2):292-3.**

18. Kampmann C, Wiethoff CM, Wenzel A, Stoltz G, Betuncor M, Wippermann C-F, Huth R-G, Hubermehl P, Khuf M, Emschermann T, Stopfkuchen H. Normal values of M mode echocardiographic measurements of more than 2000 healthy infants and children in central Europe. *Heart* **2000; 83:667-672.**

19. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, Dubourg O, Ku¨hl U, Maisch B, McKenna WJ, Monserrat L, Pankuweit S, Rapezzi C, Seferovic P, Tavazzi L, Keren A. Classification of the cardiomyopathies: a position statement from the European society of cardiology working group on myocardial and pericardial diseases. *European Heart Journal* **(2008) 29, 270–276.**

20. Lebech AM, Gerstoft J, Hesse B, Petersen CL, Kjaer A. Right and left ventricular cardiac function in a developed world population with human immunodeficiency virus studied with radionuclide ventriculography. *Am Heart J* **2004; 147:482–488.**

21. Overbeek L, Kapusta L, Peer P, de Korte CL, Thijssen JM. Daniels O New reference values for echocardiographic dimensions of healthy Dutch children. *Eur J Echocardiography* **2006: 7, 113 -121.**