Cardiac and Autonomic Evaluation in a Pediatric Population with Human Immunodeficiency Virus

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Summary

Background: Cardiac involvement in children with human immunodeficiency virus (HIV) infection is a well-known entity and occurs clinically more often in patients with advanced acquired immunodeficiency syndrome (AIDS). Autonomic dysfunction is less known, especially in children.

Hypothesis: The aim of this study was to assess the prevalence of cardiovascular abnormalities in a pediatric population with HIV. We also aimed to evaluate whether autonomic involvement occurs in the same population and is dependent on echocardiographic abnormalities.

Methods: The occurrence of echocardiographic abnormalities was evaluated in 22 children with HIV infection, and five noninvasive tests were performed to evaluate the presence of autonomic dysfunction.

Results: We found cardiac lesions in four children (18%), consisting of pericardial effusion in three children, wall motion abnormalities in three children, and acute aortic endocarditis in one child. All cardiac abnormalities were found at Stage C by Center for Disease Control (CDC) revised classification. We also found left ventricular filling pattern abnormalities consisting of E-wave maximal velocity decrease and prolonged deceleration time compatible with diastolic dysfunction. One of the five autonomic tests (Valsalva maneuver) was significantly altered, even in patients without abnormal echocardiography, suggesting mild autonomic dysfunction.

Conclusion: The study demonstrated a high prevalence of cardiac lesions in children with HIV infection and indicated the presence of autonomic dysfunction even when there are no echocardiographically detected abnormalities.

Key words: human immunodeficiency virus, pediatric population, echocardiography, autonomic function

Introduction

Early in the 1980s, cardiac disease was considered to be a rare complication of advanced infection with human immunodeficiency virus (HIV). The first observation of a Kaposi sarcoma was made in an autopsy study in 1983.¹ Cohen *et al.* reported the first cases of fatal dilated cardiomyopathy 2 years later.² Cardiac involvement is now often recognized during the course of HIV infection.³

Dysrhythmias, hemodynamic abnormalities, congestive heart failure, and sudden death are among the most serious complications.⁴ These may be due to HIV-related disease of the heart itself, but autonomic nervous system alterations may trigger some of these clinical manifestations.

Several echocardiographic studies report cardiovascular involvement in children with HIV.⁵ Much less is known about autonomic involvement in this population. Preliminary studies have shown an association between autonomic dysfunction and HIV infection in adult patients.^{6,7} Symptoms include syncope and presyncope, diminished sweating, diarrhea, bladder dysfunction, and orthostatic hypotension.

We have investigated the occurrence and clinical implications of cardiovascular abnormalities detected by echocardiography in children with HIV infection. Since autonomic dysfunction has never been specifically assessed in an HIV-infected pediatric population, and because of the increasing number of HIV-infected children,⁵ we also aimed to evaluate whether autonomic dysfunction occurs in this population, and whether this autonomic involvement is independent of echocardiographically detected abnormalities.

Materials and Methods

Patients

Between January 1995 and June 1996, 22 patients (mean age 7.8 ± 4.2 years) with documented HIV infection underwent cardiac evaluation at our institution. The mean follow-

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up duration was 6 months (range 1 day–18 months). All patients were infected vertically; 20 were referred for routine cardiac evaluation, whereas 2 were hospitalized for an acute problem at the time of evaluation. At our institution, HIV-infected children are evaluated routinely by echocardiography twice a year. Patients were classified according to the "Revised Classification System of the Center for Disease Control":⁸ 6 children were in Stage B (4 in B1, 1 in B2, and 1 in B3), and 16 were in Stage C (3 in C1, 5 in C2, and 8 in C3). Various analogues of nucleosides (zidovudine, zalcitabine) were administered to 16 patients (73%). A detailed clinical history was obtained for each patient; weight and height of all patients were recorded and body surface area (BSA) calculated using standard normograms. The protocol was approved by the Ethics Committee of our hospital and one parent of each child gave oral consent for the study.

Two-Dimensional, M-Mode Echocardiography and Doppler Examination

All patients, as well as a control group of 16 healthy children matched for age and gender, underwent complete echocardiographic examination (Toshiba SSH 380). Measurements were taken according to the criteria of the American Society of Echocardiography.⁹ The transducer frequency was 3.5 or 5 MHz, either or both being used for each patient. The examination was performed in the left lateral position whenever possible.

Cross-sectional imaging was performed from the standard parasternal, apical, and subcostal views, and transmitral flow velocity patterns were recorded from the apical four-chamber view. Pulsed Doppler recordings were obtained with the sample volume located between the tips of the mitral leaflets. Heart rate (HR) was noted for each patient. We measured peak velocity of early (E) and late (A) mitral outflow (cm/s), E/A ratio, and deceleration time of the E wave (DT in ms). The isovolumetric relaxation time (IVRT in ms), defined as the time interval between aortic valve closure and mitral opening, was averaged from three consecutive cycles. Left ventricular segmental wall motion was explored systematically using two-dimensional imaging. Wall motion abnormalities were assessed by visually evaluating wall motion and endocardial thickening of the different left ventricular wall segments, as recommended by the American Society of Echocardiography.⁹

Autonomic Function Testing

Fourteen HIV-infected children were recruited. None of these children had diabetes mellitus, neurological disorders, or other disorders known to affect the autonomic nervous system. Patients were afebrile and did not appear clinically dehydrated. No patient had an electrolyte pattern suggesting adrenal insufficiency. As patients had to be older than 4 years to be included in testing, only 14 of the 22 initially selected underwent autonomic testing. These patients were compared with a group of nine controls selected concurrently to match the age and gender of the patients. The age was 8.4 ± 3.68 years in pa-

tients with HIV and 9.4 ± 2.46 in the controls (difference not significant). We performed five noninvasive tests as recommended by Ewing *et al.*¹⁰

(1) *The Valsalva maneuver*: The seated patient was asked to expire for 15–20 s against a resistance of 20 mmHg. The Valsalva ratio (VR) (the ratio of the maximum heart rate during the expiratory phase to the minimum heart rate during the relaxation phase) was calculated.

(2) *The heart rate response to standing up (HRSU)*: The subject lies quietly on a couch and stands up unaided. Normally, an immediate increase in heart rate occurs that is maximal at about the 15th beat after starting to stand, followed by a relative bradycardia, maximal around the 30th beat. This allows to calculate the 30:15 ratio, which is the ratio of the longest R-R interval around the 30th beat to the shortest R-R interval around the 15th beat.

(3) *The heart rate response to deep breathing (DB) (beats/min)*: The subject sits quietly and then breathes deeply at 10 breaths/min. The maximum and minimum heart rates during each breathing cycle are measured, and the mean of the differences during three successive breathing cycles are taken to give the maximum-minimum heart rate.

(4) *The blood pressure response to standing up (BPSU) (mmHg)*: The difference in systolic blood pressure after standing up is measured with a standard sphygmomanometer.

(5) *The blood pressure response to sustained handgrip (HG) (mmHg)*: Blood pressure is measured each minute during a voluntary contraction of 5 min. The difference between the diastolic blood pressure (corresponding to the phase 5 of Korotkoff sounds) just before release of handgrip and before starting is taken as the measure of response.

Statistical Analysis

Data are expressed as means $\pm$ standard deviation. Comparisons between groups were performed using the Student's unpaired *t*-test. Differences between groups were considered significant at $p < 0.05$.

Results

Echocardiography (Table I)

We found a mild degree of wall motion abnormalities in three patients (14%), represented by mild septal hypokinesis, and one child (5%) had severe diffuse hypokinesis with a 30% left ventricular ejection fraction. Three patients (14%) presented with mild pericardial effusion and one child (5%) had aortic endocarditis, documented by a small aortic vegetation as well as by positive hemocultures for *Streptococcus pneumoniae*. All of these echocardiographic lesions were limited to patients in Stage C. Comparing the values of left ventricular filling parameters of the patients with those of the control group, we found that patients with HIV had decreased E-wave maximal velocity and prolonged deceleration time. The HIV carriers also had a significant increase in

TABLE I Echocardiographic results

	BSA (m ²)	HR (beats/min)	E (cm/s)	A (cm/s)	E/A	IVRT (ms)	DT (cm/s)
Control	1.03 ± 0.25	89 ± 10.4	102 ± 21	47 ± 14	2.4 ± 0.8	60 ± 13	126 ± 20
HIV	0.88 ± 0.26	96 ± 14.1	89 ± 13	48 ± 16	2.1 ± 0.8	62 ± 14	148 ± 36
p Value	NS	<0.05	<0.05	NS	NS	NS	<0.05

All data are expressed as mean ± standard deviation.

Abbreviations: BSA= body surface area, HR=heart rate, E= E wave maximal velocity, A= A wave maximal velocity, IVRT=isovolumetric relaxation time, DT= deceleration time of the E wave, NS = not significant.

TABLE II Results of the autonomic testing

	Age	V	HRSU	DB (/min)	BPSU (mm Hg)	HG (mmHg)
Control	9.4 ± 2.46	1.49 ± 0.21	1.05 ± 0.14	37.67 ± 13.1	8.89 ± 8.21	16.11 ± 5.46
HIV	8.4 ± 3.68	1.26 ± 0.15	1.09 ± 0.11	31.62 ± 9.6	7.69 ± 6.65	12.5 ± 8.66
p Value	NS	p < 0.05	NS	NS	NS	NS

Abbreviations: V= Valsalva maneuver, HRSU= heart rate response to standing up, DB=heart rate response to deep breathing, BPSU= blood pressure response to standing up, HG= handgrip test, HIV = human immunodeficiency virus, NS = not significant.

heart rate; they had no significant decrease in BSA. We know that an increase in heart rate can modify left ventricular filling patterns, with an A wave increase of 8 cm/s for each 10 beats/min increase.¹¹ In our population, the A wave was not increased despite a significant increase in the heart rate and the E wave was significantly decreased. Therefore, these differences of left ventricular filling parameters suggest diastolic dysfunction in our population.

The only child with severe alteration of the systolic function died of septic shock several days later. The other three children with pericardial effusion had repeated echocardiography 1 week later showing disappearance of the effusions. The etiology of these effusions was suspected to be infectious, even when there were no viral seroconversions and no bacterial documentation during follow-up. All these children have had an uneventful course during the 6-month follow-up period.

Autonomic Testing (Tables II and III)

Among the noninvasive tests performed, only the Valsalva maneuver was significantly altered in the patients with HIV compared with the controls. This test remained significantly altered, even after exclusion of the child with echocardiographic abnormalities. None of the children had signs or symptoms suggestive of dysautonomia such as orthostatic hypotension, syncope, or bladder dysfunction.

Discussion

Our study demonstrates that there is a high prevalence of echocardiographic abnormalities in a pediatric population with HIV, although children were mostly asymptomatic, except for one child with poor left ventricular ejection fraction

and another with endocarditis. Although studies in adults have shown that HIV carriers with pericardial effusion have a poorer prognosis,¹² we did not observe this poor evolution in our population.

The prevalence of cardiac abnormalities in the present study is slightly lower than that reported in other studies.¹³ This may be explained by the high percentage of ambulatory patients (82%) and the high CD4 count ($452.4 \pm 494.2/\text{mm}^3$). We found cardiac abnormalities only in patients in Stage C. These findings are similar to those previously reported.^{14, 15}

This is the first study to suggest autonomic dysfunction in a pediatric population with HIV compared with a control group,

TABLE III Autonomic testing: Individual data

Patient No.	Age (years)	V	HRSU	DB (/min)	BPSU (mmHg)	HG (mmHg)
1	7	1.5	1.13	29	10	10
2	7	1.12	1.23	44	5	5
3	17	1.26	1.13	18	20	5
4	8.5	1.6	0.88	40	0	10
5	4.5	1.16	1	16	0	NA
6	5	1.11	1.13	29	20	20
7	10	1.36	1.05	NA	0	30
8	4.5	NA	NA	40	NA	NA
9	13.5	1.15	0.9	29	5	20
10	8.5	1.27	1.1	26	10	20
11	4.5	1.17	1.03	32	10	0
12	11.5	1.3	1.03	32	5	15
13	9.5	1.17	1.13	27	5	10
14	7	1.21	0.88	49	10	5

Abbreviation: NA= not available. Other abbreviations as in Table II.

as measured by five noninvasive tests of the autonomic nervous system. The Valsalva maneuver was the only parameter altered in our population, suggesting mild dysautonomia and probably resulting from a predominant parasympathetic alteration as suggested by Ewing *et al.*¹⁰ We also noted a significant difference between the resting heart rate of patients with HIV infection and the control population, which may also reflect autonomic dysregulation, as observed in diabetic neuropathy. Nevertheless, as shown by Ewing *et al.*, it is unlikely that this higher heart rate affects any of the three tests involving heart rate, including the response to Valsalva maneuver.¹⁰ Our study demonstrates that there is autonomic involvement of HIV infection independent of cardiac dysfunction, detected by echocardiography, and of peripheral and central neurologic syndromes. However, we cannot exclude the possible role of subclinical myocardial dysfunction. As recently shown by Lipshultz *et al.*,¹⁶ inadequate left ventricular hypertrophic response to left ventricular dilatation may occur, and the alteration of left ventricular inflow suggested by our study may represent an early marker of these changes. Moreover, one cannot rule out a role for malnutrition or for neurotoxic medications: 73% of our patients received antiviral medication.

The clinical implication of the dysautonomia observed in our population remains unclear, as none of the children had symptoms. However, because the introduction of new therapies has dramatically changed the history of the disease, symptoms related to dysautonomia could become apparent during long-term follow-up.

The small number of patients is a limitation of our study, especially in Stage B. As almost one fifth of all Belgian pediatric patients with HIV were included in the present study, the need for a multicenter study is suggested.

Conclusion

The present study demonstrates a high prevalence of cardiac lesions in children with HIV infection. Autonomic dysfunction seems to be present even when there are no echocardiographically detected abnormalities.

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