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Pulmonary Function by Spirometry in Children with Perinatal HIV Infection

Nancy J. Gálvez[1,2], Julio W. Juárez[1,2]

[1]Pediatric Infectology Hospital Roosevelt, Guatemala, Guatemala
[2]Integrated Assistance Unit for HIV and Chronic Infections, Hospital Roosevelt "Dr. Carlos Rodolfo Mejía Villatoro", Guatemala, Guatemala
Email: nashi.jgr@hotmail.com, jwerner_juarez@hotmail.com

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Abstract

Background: In an age of antiretroviral therapy, the life expectancy of children perinatally infected with Human Immunodeficiency Virus (HIV) has significantly increased. At the same time, however, pulmonary pathologies secondary to opportunistic infections have decreased thanks to increased diagnostics and access to antiretroviral therapy (ART). Despite this, in these children an immune dysregulation is maintained due to chronic infection. There is evidence that these patients have increased probability of presenting with abnormalities in pulmonary function, mainly with chronic obstructive clinical pictures (25% - 40% of perinatally infected adolescents display some anomaly in the spirometry), which predisposes them to increased risk of chronic pulmonary disease. Since lung development occurs mainly during infancy, patients perinatally infected with HIV may suffer consequences. This can be secondary to opportunistic infections, chronic inflammation due to the virus, and immunologic effects of ART, mainly in non-industrialized countries, where late diagnosis is frequent. **Methodology:** An analytical, observational, cross-sectional study was conducted at Roosevelt Hospital Pediatric infectious disease clinic, from January to December 2019. A sample of 76 patients was obtained, out of a population of 362 patients. A total of 62 subjects, who met the criterion of reproducibility in the spirometry, were analyzed. Results were analyzed with percentages and the association of variables using the chi-squared test (χ^2). **Results:** A decrease in pulmonary function was found in 34% of patients, mild obstructive pattern (16%) predominating. Significant association between basal viral load greater than 100,000 cp/ml and a decrease in Forced expiratory flow 25 - 75 (FEF 25-75) (p 0.046) and in relationship between forced expiratory volume and forced vital capacity (FEV1/FVC p = 0.024) was observed, as well as a non-statistically significant relationship between advanced clinical stage at diagnosis and decreased pulmo-

nary function. **Conclusions:** The prevalence of decreased pulmonary function related to advanced clinical stage and elevated basal viral load (>100,000 cps/ml) is higher than that reported in other studies (25%) and has an influence in the long-term decrease in pulmonary function.

Keywords

Pulmonary Function, Perinatal HIV Infection, Spirometry

1. Introduction

The Human Immunodeficiency Virus (HIV), and its impact on the immune system make the host vulnerable to a wide range of opportunistic infections in the respiratory tract; however, with the advent of antiretroviral therapy (ART), non-infectious chronic complications are an important cause of morbidity among patients living with HIV [1] [2]. These complications include pulmonary conditions associated both to the virus itself and to the lesions produced by opportunistic infections and even ART itself. [3] [4].

Infancy and early childhood are critical periods for the development of the immune system and organs like lungs among children with perinatal infection due to HIV. The virus mediated immune dysregulation may place children at risk of pulmonary damage [5]. This has been observed in adolescent patients with perinatal HIV diagnosis and delayed initiation of ART as they have increased prevalence of chronic obstructive pulmonary disease [6] [7].

It has been proven that HIV is directly cytotoxic to alveolar macrophages with non-infected adjacent macrophages producing metalloproteinases in response. Metalloproteinases degrade the pulmonary extracellular matrix and have been proven to be important in the pathogenesis of smoking-related chronic obstructive pulmonary disease (COPD) [3] [8] [9] [10] [11]. Similarly, increases in systemic and pulmonary oxidants have been described in HIV-infected patients, which produce prolonged oxidative stress and glutathione deficiency, as well as natural antioxidant pathways infected by ART and virus itself. Systemic inflammatory markers are also elevated in HIV infection, particularly with advanced immunosuppression, which also activates alveolar macrophages, thus contributing to obstructive pulmonary disease and other pathologies [7] [12] [13].

Uncontrolled HIV viral replication has been associated with an accelerated decrease in pulmonary function. This effect is mediated by direct viral factors, but it is also enhanced secondary to opportunistic infections [7] [14].

HIV suppression through antiretrovirals leads to an increase in pulmonary tissue from multifunctional HIV-specific CD4 effector T cells, which exposes the pulmonary tissue to the inflammatory effects of immune reconstitution [13]. These effects occur in the long term, mainly in patients with late diagnosis and initiation of therapy (slow progressors), who are associated with better response

to CD8 T cells [15]. These effects can manifest themselves as episodes of bronchial hyperreactivity, chronic cough, chronic obstructive pulmonary disease, bronchiectasis, as well as pulmonary hypertension, and lymphoid interstitial pneumonitis [15] [16].

The identification of anomalies in pulmonary function is key for the comprehensive treatment of patients with perinatal HIV infection [16] [17]; however, pediatric data is scarce, mainly in Latin American populations.

This study evaluated pulmonary function through spirometry among pediatric patients with perinatal infection during clinical monitoring, analyzing variables such as viral load, immune clinical stage at the time of diagnosis, timing of ART, age at diagnosis, and history of opportunistic infections.

2. Methods

Study design: Observational analytical, cross-sectional study.

Study conducted at Roosevelt Hospital, in Comprehensive Care Unit for HIV and chronic Infections "Dr. Carlos Rodolfo Mejía Villatoro" Pediatric area, from January to December 2019. Pulmonary function was measured trough spirometry. Spirometry was performed in the Pediatric pneumology clinic of the Roosevelt Hospital, on female and male patients ages 6 - 16 with a diagnosis of perinatal HIV infection on clinical monitoring.

A random sample of 79 patients was taken out of a total of 270 by using the EPIDAT software, which has a confidence level of 95% and a sampling error of 8%.

The variables evaluated were age at diagnosis, viral load at the time of diagnosis, immune clinical stage at the time of diagnosis, and time of antiretroviral therapy. Data were obtained from clinical records. Lung function parameters obtained though spirometry were: FEV1 (Forced expiratory volume in 1 second), FVC (Forced vital capacity) FEF 25-75 (Forced expiratory flow between 25% and 75% of forced vital capacity) FEV1/FVC (Relationship between forced expiratory volume and forced vital capacity). The parameters were analyzed by Care Fusion's Spirometry PC Software (SPCS)®.

Only patients taking antiretroviral therapy and whose parents signed the informed consent were included. Patients with a history of bronchial asthma and exposure to secondhand smoke were excluded. Chi-square (X2) was used to test the relationship between variables.

This study was approved by the Roosevelt Hospital Teaching and Research committee.

3. Results

Out of 76 subjects, the spirometry failed to comply with reproducibility criteria in 14, either due to fatigue or inadequate technique; therefore, these were excluded from the analysis. Of the 62 patients included, the results obtained from spirometry are as follows: Normal 66% (n = 41), abnormal 34% (n = 21), of pa-

tients with abnormal spirometry it was found that the 33% (n = 7) whit mild restriction, 14% (n = 3) whit moderate restriction, 47% (n = 10) whit mild obstruction and 6% (n = 1) with moderate obstruction.

A total of 37.1% of patients were classified in immune clinical stage C3 (Classification of the stages of HIV infection CDC 1993) and 14.5%, in stage B2. A total of 95.2% of patients had been on ART for more than 3 years, with a mean of 7 years.

At least 14.5% of patients had a history of either pulmonary tuberculosis, lymphoid interstitial pneumonitis or mechanical ventilation. Average age of diagnosis was 3.4 years and mean age of subjects at the time of the study was 10.9 years. The average CD4+ count at the time of diagnosis was 691 cell/mm^3.

The risk factors associated with decreased lung function were high viral loads at the time of diagnosis (>100,000 cp/ml) which corresponds to active viral replication because these children had no TAR at that moment, finding a statistically significant relationship with the values of FEF 25-75 and FEV1/FVC (p = 0.046 and p = 0.024 respectively),as can be seen in Table 1, and advanced clinical stages at the time of diagnosis, which is related to late diagnoses of infection and late start of ART, with clinical correlation, but non-statistically significant relationship between this variables as can be seen in Table 2.

4. Discussion and Analysis

The Respiratory diseases represent the leading cause of morbidity and mortality among children and adolescents who are infected with HIV. The population of Sub-Saharan Africa is the most affected, since this region has the highest concentration of HIV. Studies have previously shown a significant decrease in pulmonary function (up to 25%) in HIV-infected children compared with the non-infected population [18] [19].

This study found a more striking difference, with a 34% prevalence of decreased

Table 1. Viral load (*cp/ml) at the time of HIV diagnosis and spirometry values.

		1000 - 9999		10,000 - 99,999		100,000 - 999,999		>1,000,000		Total	Value p
		f	%	f	%	f	%	f	%		
FEV1	<80	1	20.0%	2	18.2%	4	13.3%	4	25.0%	11	0.802
	>80	4	80.0%	9	81.8%	26	86.7%	12	75.0%	51	
FVC	<80	1	20.0%	2	18.2%	4	13.3%	5	31.3%	12	0.541
	>80	4	80.0%	9	81.8%	26	86.7%	11	68.8%	50	
FEF25-75	<65	3	60.0%	0	0.0%	6	20.0%	5	31.3%	14	0.046
	>65	2	40.0%	11	100.0%	24	80.0%	11	68.8%	48	
FEV1/FVC	<0.90	3	60.0%	0	0.0%	4	13.3%	4	25.0%	11	0.024
	>0.90	2	40.0%	11	100.0%	26	86.7%	12	75.0%	51	

FEV1 = Forced expiratory volume in 1 second. FVC = Forced vital capacity. FEF25-75 = Forced expiratory flow between 25% and 75% of forced vital capacity. FEV1/FVC = Relationship between forced expiratory volume and forced vital capacity. F = frequency, *cp/ml = copies per milliliter of blood.

Table 2. Clinical stage at the time of HIV diagnosis and spirometry values.

		*N		A		B		C		Value *p*
		f	%	*f*	%	*f*	%	f	%	
FEV1	<80	0	0.0%	1	14.3%	3	17.6%	7	22.6%	
	>80	6	100.0%	6	85.7%	14	82.4%	24	77.4%	0.200
FVC	<80	0	0.0%	1	14.3%	3	17.6%	8	25.8%	
	>80	6	100.0%	6	85.7%	14	82.4%	23	74.2%	0.134
VEV1/FVC	<0.90	2	33.3%	2	28.6%	3	17.6%	4	12.9%	
	>0.90	4	66.7%	5	71.4%	14	82.4%	27	87.1%	0.164
FEF25-75	<65	1	16.7%	2	28.6%	4	23.5%	7	22.6%	
	>65	5	83.3%	5	71.4%	13	76.5%	24	77.4%	0.960

FEV1 = Forced expiratory volume in 1 second. FVC = Forced vital capacity. FEF25-75 = Forced expiratory flow between 25% and 75% of forced vital capacity. FEV1/FVC = Relationship between forced expiratory volume and forced vital capacity. F = frequency. *Classification of the stages of HIV infection CDC 1993.

pulmonary function in our population. A mild obstructive pattern was the most frequent form of alteration in the spirometry (16%), as opposed to other studies that have reported 20% - 25% of HIV-related pulmonary disease [19] [20]. A factor that may influence our environment is the late diagnosis of HIV infection, since 37% of the subjects were classified in stage C3 at the time of diagnosis.

Viral load is an important variable among the pediatric population, which is characterized as having high viral loads for prolonged periods, thus promoting a state of chronic inflammation due to uncontrolled viral replication [21]. This has been associated with an accelerated decrease in pulmonary function mediated by the direct action of the virus and opportunistic infections [3]. When comparing viral load values with pulmonary function, patients with values greater than 100,000 cp/ml were found to have a more deteriorated pulmonary function, although this was not statistically significant ($p = 0.073$).

Table 1 shows the relationship between the spirometry parameters and the viral load at the time of patient's diagnosis, observing statistically significant relationship in patients with viral load greater than 100,000 copies and a decrease in FEF 25-75 in the spirometry (p 0.046), which indicates a precocious condition. FEF 25-75 measures the flow's alteration in medium and small caliber airways and contributes information regarding the amount of total exhaled air in the period between 25% and 75% of exhalation. Normal values are greater than 60% and is considered a precocious marker of damage in small and medium airways, in such a way that it can be altered long before other spirometric data [22] [23].

Table 2 shows the pulmonary function variable compared with clinical stage at the time of diagnosis; A clinically significant correlation was found, as patients who were diagnosed in clinical stage C received abnormal results in the spirometry more frequently; however, the finding was not statistically significant ($p = 0.200$ for FEV1 and $p = 0.134$ for FVC). The above is due to the fact that the

progress of the infection at early ages and the late initiation of antiretroviral therapy result in the cytotoxic activity of alveolar macrophages, which leads to oxidative stress and the perpetuation of inflammation, thus producing abnormalities in the flow of exhaled air [21] [24]. However, when pulmonary function was compared with immunological stage shown in **Table 3**, no statistically significant relationship was found. This may be due to the variability in the number of T CD4, mainly in children under 6. In addition, at this age, the number of T CD4 is not necessarily correlated with the functionality of these cells. ($p = 0.61$ for FEV1, $p = 0.49$ for FVC, $p = 0.56$ for FEV1/FVC, $p = 0.96$ for FEF 25-75). Regarding the background of pulmonary condition associated with HIV, such as tuberculosis, lymphoid interstitial pneumonitis, and mechanical ventilation, no significant relationship with the results of the spirometry was found. This may be due to the few cases observed.

A total of 95.2% of the patients had received antiretroviral therapy for more than 3 years, with an average of 7 years of treatment. A correlation with lung function cannot be established with these data, since only 3 patients had less than 1 year of treatment, due to the fact that a normal distribution of the data was not obtained.

The main limitation of the study is that healthy subjects were not included as a control group.

5. Conclusions

Decreased pulmonary function was prevalent in 34% of patients in this study, and a mild obstructive pattern was the most frequent form of alteration in the spirometry in 16% of cases.

Viral loads greater than 100,000 copies/mm^3 are associated with decreased pulmonary function, which was observed mainly in FEF 25-75.

A clinically significant relationship was found between clinical stage at the

Table 3. Immunological stage at the time of HIV diagnosis and spirometry values.

		1		2		3		
		f	%	*f*	%	*f*	%	Value p
FEV1	<80	2	15.4%	3	16.7%	6	20.0%	
	>80	11	84.6%	15	83.3%	24	80.0%	0.61
FVC	<80	2	15.4%	5	27.8%	5	16.7%	
	>80	11	84.6%	13	72.2%	25	83.3%	0.497
FEV1/FVC	<0.90	3	23.1%	5	27.8%	3	10.0%	
	>0.90	10	76.9%	13	72.2%	27	90.0%	0.566
FEF25-75	<65	4	30.8%	4	22.2%	6	20.0%	
	>65	9	69.2%	14	77.8%	24	80.0%	0.967

FEV1 = Forced expiratory volume in 1 second. FVC = Forced vital capacity. FEF25-75 = Forced expiratory flow between 25% and 75% of forced vital capacity. FEV1/FVC = Relationship between forced expiratory volume and forced vital capacity. F = frequency.

time of diagnosis (stage C) and decreased pulmonary function; however, this was not statistically significant.

No relationship was found between immunological stage at the time of diagnosis and pulmonary function.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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