ORIGINAL ARTICLE

Fat redistribution and metabolic disturbances in HIV-infected children and adolescents under highly active antiretroviral therapy (HAART)

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Abstract

Background. Morbidity and mortality associated with human immunodeficiency virus (HIV) infection has decreased since the introduction of highly active antiretroviral therapy. Unfortunately, treatment has been associated with metabolic disorders, lipodystrophy syndrome (LDS) characterized by loss of fat, dyslipidemia and glucose intolerance. This study was conducted in a pediatric outpatient clinic and included children and adolescents infected with HIV/acquired immunodeficiency syndrome (AIDS) aged from 2 to 18 years.

Methods. Total cholesterol, triglycerides and fasting glucose were measured. Patients were evaluated based on characteristics associated with LDS.

Results. Ninety two children and adolescents infected with HIV were included; 51% of patients had hyperlipidemia and 16% showed evidence of fat redistribution. A significant percentage (54%) of HIV-infected children and adolescents developed changes in metabolic parameters or fat redistribution. Hypertriglyceridemia and peripheral lipoatrophy were the most frequent alterations.

Conclusions. Although widely described in adults infected with HIV, reports of LDS in children are rare. Future research lines in children and adolescents infected with HIV/AIDS may determine the therapeutic strategies for the management of LDS in children.

Key words: HIV, infection, children, cholesterol, triglycerides, lipodystrophy.

Introduction

The epidemic infection of the human immunodeficiency virus (HIV) in children and adolescents has changed substantially during recent years, since the introduction of highly active antiretroviral therapy (HAART) in routine clinical use. Morbidity and mortality associated with HIV infection has decreased dramatically. In the U.S. between the years 1995 and 1999, the annual number of deaths decreased by 67%, coincident with the implementation of HAART.[1] However, antiretroviral drugs (ARVs) are not free from side effects, toxicity and interactions with other drugs.[2,3] Among these complications, lipodystrophy syndrome (LDS), mitochondrial toxicity and, more recently, abnormalities in bone metabolism are some of the side effects of prolonged ARV therapy.[4,5] HAART has recently been reported to include protease inhibitors (PI). It may be associated with early onset of metabolic syndrome in children, which is a predisposition to future cardiovascular risk.[3]

LDS is not well defined and includes fat redistribution and metabolic abnormalities. It was initially described in adults in relation to the introduction of PI and has recently been reported in children infected with HIV.[6,7] The incidence of moderate to intense physical changes in adult patients whose

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initial plan includes HAART is 5% during the first year of treatment and 25% in the second year. The prevalence of these changes in the pediatric population infected with HIV varies between 1 and 75% during ARV treatment, although more recent studies describe it as 25-30%.[7]

Clinically, there are three patterns of fat redistribution. The most prominent clinical sign is the loss of subcutaneous facial fat (periorbital, temporal), extremities and buttocks, as well as the presence of prominent veins or lipoatrophy. In addition to the central accumulation of fat in the abdomen, posterior neck (buffalo hump) and breast or lipohypertrophy, a mixed form exists with thin extremities and central fat accumulation. Children may present little fat redistribution after initiation or change of ARV therapy.[8]

Patients are often the first to identify the clinical symptoms by observing changes in their facial features or with their clothing. These changes are not only aesthetically undesirable, but they also predispose to future cardiovascular diseases and type 2 diabetes mellitus, not to mention the psychological disorders that may lead to poor adherence to treatment.[4]

The etiopathogenesis of this condition is multifactorial. Different studies have described the association between lipohypertrophy with data including PI, age, female gender, elevated viral load, duration of ARV therapy and high body mass index (BMI), and association between lipoatrophy and low BMI, data that include stavudine, and severity and duration of HIV infection. These factors may be directly implicated or associated with other types of environmental factors such as diet, exercise and genetics, which influence in a currently unknown manner.[7]

HIV infection itself is associated with dyslipidemia, low levels of high-density lipoproteins and an increase in the values of total cholesterol (TC), triglycerides (TG) and low-density lipoproteins.[9] The change in lipid profile is associated with the use of ARV, particularly with the PI but also with the non-nucleoside reverse transcriptase inhibitors (NNRTIs) in adult patients.[10,11]

Long-term consequences that include increase in the values of TC or TG in the pediatric population have not been determined and are, at present time, speculative.

Dietary changes and weight loss, as part of an overall plan for reduction of cholesterol, can be difficult in children. Because of the importance that this can have in this population, prophylactic treatment with a diet and healthy lifestyles should be part of the systematic treatment for HIV-infected children from the first months of life and before ARV therapy can be initiated.[3]

Methods

A transverse and descriptive study took place in the Clinic for Children with HIV/Acquired Immunodeficiency Syndrome (AIDS) of the National Autonomous University of Mexico in Mexico City. We included children and adolescents infected with HIV between the ages of 2 and 18 years with no conditions of AIDS and under combined ARV treatment. The following variables were recorded: patient age, gender and characteristics of the HIV infection. Relevant history was obtained for the use of ARV from the clinical files.

Laboratory studies included TC, TG, and fasting serum glucose (FSG), which were obtained routinely every 3 months. Hyperlipidemia was defined as the presence of TC >200 mg/dL or TG >150 mg/dL; the criteria for defining hypercholesterolemia was taken from fasting cholesterol values in children of the National Cholesterol Education Program.[12]

Routine physical examination was performed by a physician who assessed fat loss in the extremities, buttocks and face, in addition to the accumulation of fat in the abdomen and dorsocervical spine. Fat redistribution is defined as lipoatrophy, lipohypertrophy or mixed pattern, according to the classic clinical features described in the literature.[13]

a) Lipoatrophy-loss of facial fat, thinner limbs with prominent veins, with or without atrophy of buttocks

b) Lipohypertrophy-increased abdominal volume, increase in breast size, with or without a buffalo hump and lipomas

c) Mixed pattern-increased abdominal size, breast, sunken cheeks and thinner extremities with prominent veins, with or without a buffalo hump and atrophy of buttocks

Results

We included 92 children and adolescents infected with HIV. Ages ranged from 2-18 years of age. All patients were clinically stable at the time of the study.

According to the classification of the disease by the Centers

Table 1. Clinical characteristics of children and adolescents infected with HIVI under HAART and under surveillance at the Clinic for Children with HIV/AIDS (UNAM, 2008)

Variable	LDS (n = 15)	No LDS (n = 77)
Age (years)	11.5	8.7
Gender (F/M)	8/7	40/37
Clinical stage C	5	30
Immune stage 3	0	0
CD4+ (cells/mL)	947	1 076
Viral load <50 copies	11	67
Duration of ARV (years)	7.24	5.2
Number of schemes	2.4	1.6

UNAM, National Autonomous University Mexico; HAART, highly active antiretroviral treatment; LDS, lipodystrophy syndrome; ARV, antiretroviral;

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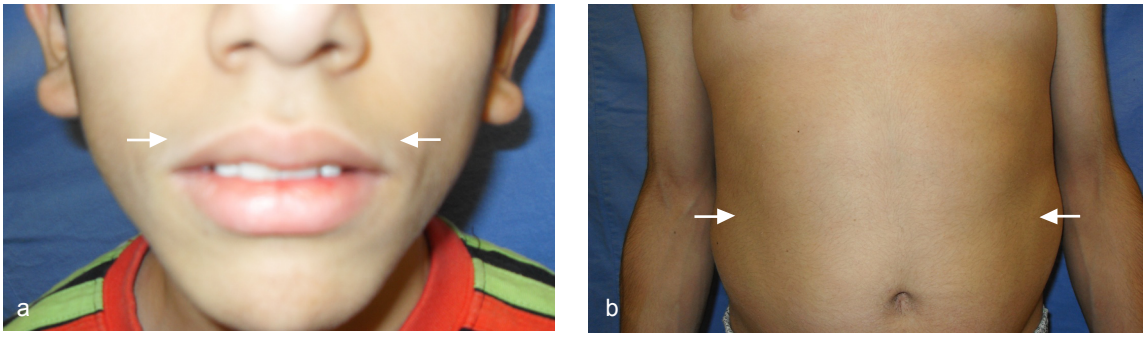

Figure 1. Eleven-year-old male patient with facial lipoatrophy (a) and central obesity (b).

for Disease Control and Prevention (CDC), at the time of admission the patients were in the following clinical stages: 30 in stage A, 27 in stage B, and 35 in stage C. With respect to the total or percentage of CD4+ cells, 80 patients were in stage 1 and 12 patients were in stage 2. There were no patients in stage 3.

In the group of patients studied, 100% of patients received a combination ARV therapy: 88% with treatment of 2 ITRAN + 1 PI and 12% with 2 ITRAN + 1 NNRTI.

In general, the average time for ARV treatment in the study group was 5.5 years, with an average of 1.7 ARV treatments; 53% of patients were in the first scheme. Information for patients with and without clinical evidence of lipodystrophy is shown in Tables 1 and 2.

LDS was observed in 15 (16%) of the 92 patients. The most common pattern was lipoatrophy (60%), followed by a mixed pattern (40%) (Figure 1). The average age of these children was 11.5 years (range: 5.4-17.7 years). There were eight girls and seven boys. In this group of children the average time of ARV treatment was 7.24 years, with an average of 2.4 treatments. Forty percent of patients presented hypertriglyceridemia and 34% presented with hypercholesterolemia. We observed hypercholesterolemia along with hypertriglyceridemia in 27% of patients.

In the group of patients without lipodystrophy, the average age was 8.7 years. There were 40 females and 37 males in the group. The mean length of time of ARV was 5.2 years, with an average of 1.6 treatments; 35% of the patients had hypercholesterolemia, 36% had hypertriglyceridemia and 18% of patients showed hypercholesterolemia along with hypertriglyceridemia.

FSG levels were normal for all patients with the limitation that a glucose tolerance test was not performed.

Discussion

LDS is a frequent complication in children and adolescents infected with HIV/AIDS. In this group, the average age of children infected with HIV was 9.1 years. This reflects the use of various ARV regimens and a cumulative exposure to drugs that will continue for the nature of the disease.

Even now, after years of its first de scription, there is still no consensus on a definition of LDS in pediatric patients infected with HIV, which is reflected in the prevalence reported in various studies (0-67%).[14,15]

A significant percentage (54%) of patients in this study developed changes in metabolic parameters or

redistribution of fat. The prevalence of fat redistribution in our group (16%) is less than that reported in the worldwide literature.13 However, it is important to note that in our environment it is difficult to assess lipodystrophy because diagnosis continues to be principally clinical and relatively subjective. Although there are useful techniques in the diagnostic procedure such as computed axial tomography (CAT), magnetic resonance (MR), ultrasound (US) and other techniques such as bioimpedanciometry and densitometry X-ray (DEXA),16 these are not performed routinely in our environment. In some cases, these resources are unavailable. In this study, the most common pattern of lipodystrophy was lipoatrophy, which was observed more frequently in adolescents. These patients had the greater number of years of exposure to ARV and the greater number of ARV treatments in comparison to patients who did not develop lipodystrophy. These findings were in agreement with those reported in the literature.[13,17-19]

In addition to the physical changes, we observed a high frequency of metabolic alterations. It is important to note that hypertriglyceridemia was more common that hypercholesterolemia in children with lipodystrophy, which has been reported by other authors.7,20 In children with and without lipodystrophy, hypercholesterolemia was present in ~35% of cases.

The literature in relation to LDS of HIV-infected pediatric patients is becoming more extensive, but the cause and natural history have not been well described, and the risk factors in this group have not been defined. At the beginning of the data review, we were expecting to find a higher frequency of dyslipidemia in the group studied because most of these patients have a diet rich in saturated fats as well as a sedentary lifestyle, along with a genetic tendency in the Mexican population for metabolic syndrome. Even so, we found that the frequency of dyslipidemia was consistent with that reported in the literature. Frequency for the redistribution of fat in the group studied was lower than that reported by other authors. However, regarding this last finding, there is a study of 24 Mexican children and adolescents in which there were no cases of lipodystrophy, with an elevated frequency for hypercholesterolemia and hypertriglyceridemia (62.5% and 79.2%, respectively).[14]

In one of the initial reports of lipodystrophy in children, Amaya et al.17 described 65% of LDS in patients infected with HIV, associated with the use of adult doses of ARV in the pediatric group. In other publications, an association between duration of treatment and development of lipodystrophy was not considered.[21]

Initial reports described the relationship between age and use of PI.18 Ramos found 75% of a cohort of 52 children on HAART. They had a cholesterol level >200 mg/dL, and 40% had a TG level >170 mg/dL. In this cohort, lipid abnormalities were similar in both children with and without LDS.

Cursi et al.[19] observed LDS in 46% of their sample and found hypercholesterolemia to be the most prevalent metabolic disorder. Lipodystrophy was associated with hypertriglyceridemia but not with hypercholesterolemia. Other studies describe frequencies of metabolic alterations similar to those found in this study. Jaquet et al.13 observed lipodystrophy in 33% of their population and described hypercholesterolemia as a more frequent alteration (23%) than hypertriglyceridemia (15%) in children with clinical lipodystrophy; 23% of the children without lipodystrophy had dyslipidemia.

Mellado et al.[22] reported that approximately one third of HIV-infected children under ARV therapy showed clinical evidence of LDS. This was associated with the use of PI and the duration of ARV therapy.

Lainka et al.[20] observed dyslipidemia in HIV-infected children on ARV therapy with PI, reporting that 47% had hypercholesterolemia and 65% had hypertriglyceridemia. This study found an association between the use of PI and the development of dyslipidemia. Other authors reported the frequency of hypercholesterolemia in 38% of their study population and clinical redistribution of fat in 23%.[23]

In a European study group of LDS in pediatric patients24 that included 477 children and adolescents infected with HIV, an incidence of LDS was described in 26%, with prevalence of hypercholesterolemia and hypertriglyceridemia in 27% and 21%, respectively. Metabolic alterations were present in 31% of patients with LDS, stressing that although lipodystrophy and other alterations may accompany and not necessarily present simultaneously.

In 2005, Sanchez-Torres et al. observed LDS in 26% of the population studied, with a high frequency of hypercholesterolemia (57%) and hypertriglyceridemia (71.4%). However, the laboratory used to test for hyperlipidemia had reference values lower than what is reported in previous studies. They found that the redistribution of fat was associated with age, duration of

ARV therapy, and use of HAART, as well as the presence of hypertriglyceridemia.

Of the diverse studies of children and adolescents, it is concluded that the prevalence of metabolic and clinical alterations varies according to several authors. Some of the most important factors for this variation are sample size and making a diagnosis with different criteria, along with the use of different ARV therapies. Diet and exercise are part of an overall program to reduce cholesterol, but in our study we did not have a specific dietary program for dyslipidemia in this patient group. Some drugs that were used successfully in adults were statins; however, their use in pediatrics has been limited to familial hypercholesterolemia. Currently, there are recommendations for the use of two statins in children and adolescents under HAART, pravastatin (preferred) and atorvastatin (alternative).[25] Likewise, other options such as fibrates have been described; however, they have serious drug interactions with statins and are not approved for use in children.

Inhibitors of cholesterol absorption in conjunction with statins and diet have only been used in patients >10 years of age. Psyllium and fish oil are becoming important dietary elements and are safe and well tolerated.[25] Pharmacological intervention for the treatment of hypercholesterolemia and hypertriglyceridemia is the substitution of PI by nevirapine or efavirenz, although this does not reverse the physical effects of lipohypertrophy26 and may sometimes be accompanied by a rebound in the viral load.[27]

Independent of the prevalence of LDS, its medical significance is not in question, and long-term complications of dyslipidemia are of great concern given the number of children infected with HIV and prolonged survival rate due to ARV management. Future research is necessary in the HIV-infected pediatric population with the objective of determining optimal therapeutic strategies to control the lipid profile and the prevention of LDS in HIV-infected patients, due to their pharmacological treatment.[28]

References

1.Selik R, Lindergren ML. Changes in deaths reported with human immunodeficiency virus infection among United States' children less than thirteen years old, 1987 through 1999. Pediatr Infect Dis J 2003;22:635-641.

2.Bitnum A. Serum lipids, glucose homeostasis and abdominal adipose tissue distribution in protease inhibitor-treated and naïve HIV-infected children. AIDS 2003;17:1319-1327.

3.Nuñez-Cuadros E, Mellado-Peña MJ, Rivera-Cuello M, et al. Toxicidad de fármacos antirretrovirales en niños infectados por el virus de la inmunodeficiencia humana. An Pediatr (Barc) 2008;68:425-431.

4.Leonard E, McComsey G. Metabolic complications of antiretroviral therapy in children. Pediatr Infect Dis J 2003;22:77-84.

5.Piliero P, Gianoukakis A. Ritonavir-associated hyperparathyroidism, osteopenia and bone pain. AIDS 2002;16:1565-1566.

6.Wedekind C, Pugatch D. Lipodystrophy syndrome in children infected with human immunodeficiency virus. Pharmacotherapy 2001;21:861-866.

7.Sánchez-Torres AM, Muñoz-Muñíz R, Madero R, Borque C, García MJ, de José-Gómez MI. Prevalence of fat redistribution and metabolic disorders in human immunodeficiency virus-infected children. Eur J Pediatr 2005;164:271-276.

8.Behrens GM, Stoll M, Schmidt RE. Lipodystrophy syndrome in HIV infection: what it is, what causes it and how can it be managed? Drug Saf 2000;23:57-76.

9.Kulasekaram R, Peters BS, Wierzbicki A. Dyslipidaemia and cardiovascular risk in HIV infection. Curr Med Res Opin 2005;21:1717-1725.

10.Triodras S, Mantzoros C, Hammer S, Samore M. Effects of protease inhibitors on hyperglycemia, hyperlipidemia and lipodystrophy: a 5-year cohort study. Arch Intern Med 2000;160:2050-2056.

11.Saves M, Raffi F, Capeau J, et al. Factors related to lipodystrophy and metabolic alterations in patients with human immunodeficiency virus infection receiving highly active antiretroviral therapy. Clin Infect Dis 2002;34:1396-1405.

12.National Institutes of Health. National Cholesterol Education Program, ATP III Guidelines At-A-Glance Quick Desk Reference. Bethesda, MD National Heart, Lung and Blood Institute; 2001.

13.Jaquet D, Levine M, Ortega-Rodríguez E. Clinical and metabolic presentation of the lipodystrophic syndrome in HIV-infected children. AIDS 2000;14:2123-2128.

14.Solórzano-Santos F, Goicochoa-Rangel L, Palacios-Saucedo G, Vázquez-Rosales G, Miranda-Novales G. Hypertriglyceridemia and

hypercholesterolemia in human immunodeficiency virus-1-infected children treated with protease inhibitors. Arch Med Res 2006;37:129-132.
15.Aurpibul L, Puthanakit T, Lee B, Mangklabruks A, Sirisanthana T, Sirisanthana V. Lipodystrophy and metabolic changes in HIV infected children on non nucleoside reverse transcriptase inhibitor based antiretroviral therapy. Antivir Ther 2007;12:1247-1254.
16.Polo AR, Galindo BMJ, Martínez CE, Álvarez DJ, Recomendaciones de GEAM/SPNS sobre el tratamiento de las alteraciones metabólicas y morfológicas en el paciente con infección por VIH. Enferm Infecc Microbiol Clin 2006;24:96-117.
17.Amaya R, Kozinetz C, McMeans A, Kline M. Lipodystrophy syndrome in human immunodeficiency virus-infected children. Pediatr Infect Dis J 2002;21:405-410.
18.Farley J, Gona P, Crain M, Cervia J. Prevalence of hypercholesterolemia and associated risk factors among perinatally HIV-infected children (4-19 years) in PACTG 219C. 10th Conference of Retroviruses and Opportunistic Infections. Abstract 773. Boston, MA; 2003.
19.Cursi L, Fodo L, Cancrini C, et al. Evaluation of lipodystrophy in children and adolescents treated with HAART. Abstract TuPeB4523. XIV International AIDS Conference. Barcelona: July 7-12, 2002.
20.Lainka A, Oezbek S, Falck M, et al. Marked dyslipidemia in human-immunodeficiency virus-infected children on protease inhibitor-containing antiretroviral therapy. Pediatrics 2002;110:998-999.
21.Meneilly G, Forbes J, Peabody D, et al. Metabolic and body composition changes in HIV-infected children on antiretroviral therapy. Abstract 650. In: Eighth Conference on Retroviruses and Opportunistic Infections. Chicago: Foundation for Retrovirology and Human Health; February 4-8, 2001.
22.Mellado MJ, Villota J, García M. Lipodystrophy syndrome in HIV-infected children. Abstract TuPeB4635. XIV International AIDS Conference. Barcelona: July 7-12, 2002.
23.Bockhorst J, Ksseiry I, Toye M, et al. Evidence of human immunodeficiency virus-associated lipodystrophy syndrome in children treated with protease inhibitors. Pediatr Infect Dis J 2003;22:463-465.
24.European Paediatric Lipodystrophy Group. Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe. AIDS 2004;18:1443-1451.
25.Guidelines for the use of antiretroviral agents in pediatric HIV infection. 2008 February. Available at: http://aidsinfo.nih.gov/contentfiles/PediatricGL_SupIII.pdf
26.Hansen BR, Haugaard SB, Iversen J, et al. Impact of switching antiretroviral therapy on lipodystrophy and other metabolic complications: a review. Scand J Infect Dis 2004;36:244-253.
27.Martínez E, Arnaiz JA, Podzamczer D, et al. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. N Engl J Med 2003;349:1036-1046.
28.Kamin D, Hadigan C. Hyperlipidemia in children with HIV infection: an emerging problem. Expert Rev Cardiovasc Ther 2003;1:143-150.