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Lipodystrophy among Children Infected with Human Immunodeficiency Virus and on Antiretroviral Treatment in Ouagadougou

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Abstract

Management of Human Immunodeficiency Virus infection remains a major challenge in many sub-Saharan African countries. Antiretroviral drugs which have reduced significantly the mortality rate of this pandemic disease are a source of side effects. Among these side effects, adult lipodystrophy has already been described by several authors. The aim of this study is to determine the prevalence of lipodystrophy and associate factors in children on antiretroviral therapy, managed at Charles De Gaulle Children University Hospital and Yalgado Ouedrago University Hospital in Ouagadougou, Burkina Faso. This is a cross-sectional study conducted from June 2013 to January 2014. We included children aged 2 to 15 years who had been on antiretroviral treatment for at least six months with no severe acute malnutrition (wasting). Lipodystrophy was diagnosed clinically after assessment of morphological changes. Overall, 323 children complying with the inclusion criteria were examined. The average duration of antiretroviral therapy was 5.3 years. Forty five children had lipodystrophy, *i.e.* 13.9% prevalence rate. One hundred and twenty seven different lipodystrophic lesions were noted, hence 82.7% lipoatrophy and 17.3% lipohypertrophy. The most common presentations were: face (32%), lower limbs (26%) and upper limbs (15.7%). Factors associated with lipoatrophy were: age above 10 years (P = 0.004); male gender (P = 0.0004); antiretroviral treatment duration of more than 60 months (P < 0.001) and treatment with stavudine (P = 0.01). Our study showed that lipodystrophy is not exceptional in children on antiretroviral therapy in Ouagadougou. However, more researches on lipid profiles of these children are necessary to prevent other common complications related to fat accumulation.

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Keywords

HIV, Children, Lipodystrophy, Burkina-Faso

1. Introduction

Lipodystrophy is a condition characterized by morphological changes due to a disorder in the distribution of fat in Human immune deficient virus (HIV) infected people treated with antiretroviral therapy. It remains a major issue because of the psychosocial stigma [1] and the atherogenic risk [2]-[4].

A prevalence rate of 20% to 80% has been reported [5] [6]. Several authors have shown that lipid disorders due to the long term antiretroviral use, notably hypertriglyceridemia and dyslipidemia [6]-[9].

Dollfus *et al*. in France in 2001 found 13 cases of lipodystrophy in 39 children under antiretroviral therapy. These children were aged 5 to13 years [10].

Piloya *et al.* in Uganda found in a study including 364 HIV-infected children and under antiretroviral treatment, 27% of lipodystrophy and 34% of hyperlipidemia [11].

The European group found through a study including 477 children in 30 pediatric clinics, 26% of lipodystrophy among which 8.8% of lipohypertrophy, 7.55% of lipoatrophy and 9.64% for the mixed form [12].

Nucleoside inhibitors of the reverse transcriptase are the most responsible of lipodystrophy [2] [13]. In 2013, less toxic regimens were not widely available for children in Burkina Faso [14]. Our aim is to describe lipodystrophy cases and to determine associated factors in children on antiretroviral therapy in two hospitals of Ouagadougou.

2. Materials and Method

This is a descriptive and analytical cross-sectional study. We included HIV-infected children on antiretroviral therapy managed as outpatients at Charles De Gaulle University Hospital (CHUP CDG) and Yalgado Ouedraogo University Hospital (CHUYO). The two hospitals together manage a population of 891 HIV infected children and among them 606 were on antiretroviral therapy.

Children who were on antiretroviral therapy for at least 6 months and aged between 2 and 15 years were included. A parent's or tutor's consent was required for all children to participate in the study. We excluded children who had severe malnutrition or other chronic diseases (carditis, kidney failure, tuberculosis, etc.).

Data on clinical symptoms were collected on each medical visit. Weight and height were assessed in order to check for any morphological changes. We paid special attention to fat loss areas (lipoatrophy), notably arms (thinning and decrease in the upper arm circumference), legs (thinning with abnormal visualization of veins), face (widening of cheeks or the temporal region) and buttocks (flattening). Areas of lipohypertrophy or fat accumulation were investigated on the abdomen (increase of the volume with an enlargement of waist size), chest, breast, pelvis, and neck (buffalo hump). Blood pressure assessment at rest completed the examination.

Each child's blood tests of less than 3 months were registered. Blood samples were taken on an empty stomach and then analyzed in each hospital's laboratory. Lipids measurement included only total cholesterol and tryglyceridemia. Antiretroviral treatments at admission and at the time of the survey were registered.

In our study, were analyzed antiretroviral (ARV) regimens those including the start of antiretroviral therapy, zidovudine (AZT), stavudine (D4T) or protease inhibitors (IP). Protease inhibitor available in both hospitals for the monitoring of children was ritonavir-boosted lopinavir (lopi/rt).

Data were entered and processed with Epi Info software, version 3.5.1, SPSS Version 17, Word and Excel 2007. Chi^2 statistical test was used to compare variables. Statistical gaps were significant when $P < 0.05$.

Factor analysis consisted in comparing (using Chi^2 test) the frequency of some of the characteristics between the group of children with lipodystrophies and those without. These characteristics included age, gender, treatment regimen at admission, the length of the treatment and the WHO clinical level at admission. The same characteristics (except clinical level) were compared for lipoatrophy.

3. Results

3.1. Population Description

Overall 323 children who met the inclusion criteria were examined. The average age was 9.9 years and 167 of

them (51.7%) were above 10 year-old. Male represented 50.2%.

Children were HIV1 infected in 98.8% cases (N = 319) and HIV2 in 1.2% cases (N = 4).

At the initiation of antiretroviral therapy, TCD4 lymphocytes count was available for 135 children, among them 38.5% had severe immune deficiency (TCD4 lymphocytes rate <200 cells/mm³).

Body mass index (BMI) was calculated in 289 children aged above five years and nine of them (3.1%) were obese (BMI > 30).

One hundred and sixty four (164) children had reached puberty and among them 111 (67%) were above Tanner stage 2.

Six children (2.1%) out of 282 who had their blood pressure checked, were found to have high blood pressure.

The average duration of antiretroviral therapy was 55.9 months ± 15 months with extremes of 7 and 121 months.

All the patients were on Highly Active Antiretroviral Therapy (HAART). First line treatments included the association of "zidovudine-lamivudine-nevirapine" or "stavudine-lamivudine-nevirapine" respectively in 34.7% and 30.7% of our patients.

Other characteristics of children on antiretroviral treatment are listed in **Table 1**.

At the time of the survey, among 152 children who had their blood tests available, hyperglycemia (>7.1 mmol/l) was noted in 3 children (2%); total hypercholestérolemia (>4.5 mmol/l) in 9 children (6%) and hypertrigly-ceridemia (>1.55 mmol/l) in 12 children (7.9%).

Lipodystrophy was found in 45 (13.9%) children out of 323 examined, among them 29 (62.2%) were male.

3.2. Types and Locations of Lipodystrophy

Among 45 children who had lipodystrophy, 10.8% had lipoatrophy, 1.9% had mixed type and 1.2% had lipohypertrophy.

Several locations of lipodystrophy were noticed. Some of the children presented more than one location. On the whole, 127 lesions were found in 45 children, including 82.7% of lipoatrophy and 17.3% of lipohypertrophy.

Table 2 summarizes the distribution of lipodystrophy per type and location.

The face and limbs (upper and lower) were the most common locations both for lipodystrophy and lipoatrophy.

Table 1. General characteristics of 323 children on antiretroviral therapy.

Characteristics	Number (n)	Percentage (%)
Age (years)		
≤10	156	48.3
>10	167	51.7
WHO Clinical stage*		
Stage 1	3	0.9
Stage 2	61	18.9
Stage 3	234	72.5
Stage 4	25	7.7
Social status		
Orphan**	210	65.0
Non orphan	113	35.0
Treatment duration		
≤60 mois	189	58.5
>60 mois	134	41.5
Initial Treatment regimen		
AZT+	178	55.2
D4T+	139	43.0
Other regimens	6	1.8

*WHO 2013 Classification, **orphan of one or two parents. (AZT+) = regimen containing zidovudine (AZT), (D4T+) = regimen containing stavudine (D4T).

Table 2. Distribution of lipodystrophy per type of location.

Locations	Lipoatrophy	Lipohypertrophy	Number (n)	Percentage (%)
Face	41	0	41	32.2
Lower limbs	33	0	33	26.0
Upper limbs	20	0	20	15.7
Buttocks	10	2	12	9.4
Abdomen	0	10	10	7.9
Breast	0	5	5	4.0
Brain area	1	2	3	2.4
Pubis	0	3	3	2.4

3.3. ART Regimens of Children Presenting with Lipodystrophy

Among the children presenting with lipodystrophy, 35 (77.8%) started their treatment with D4T and 9 (20%) with AZT. At the time of the survey, AZT was used in 34 (75.6%) patients, D4T in four (8.9%) patients and protease inhibitors in 12 (26.7%).

3.4. Associated Factors

We studied on one hand, the association between lipodystrophy and some of the clinical and therapeutic factors, and on the other hand, the association between lipoatrophy and the same factors listed above. Results are shown on **Table 3** and **Table 4**.

The frequency of lipoatrophy was significantly higher in patients whom antiretroviral treatment duration was more than 60 months and those whose treatment included stavudine.

4. Discussion

Patients' mean age was 9.9 years. This was also the case for Piloya in Uganda, Dollfus in France and Vigano in Italy, who recorded a mean age of 9.8 years; 9.1 years and 9.78 years in their studies respectively [10] [11] [15].

Inefficient programs for the prevention of mother-to-child transmission of HIV (PMTCT) may explain our results. The extension of the PMTCT program started in 2006 in Burkina Faso. Therefore, the majority of children born before 2006 did not benefit from this program; this accounts for the predominance of above 10 year-old patients in our study.

The first line treatment used in our study is that recommended in Burkina Faso [14].

AZT and D4T have long been the basis of the first line antiretroviral treatment in most developing countries. The process of switching D4T to AZT was done in keeping with D4T switching plan recommended by World Health Organization (WHO) in 2010 [16].

To reduce the occurrence of new cases of lipodystrophy this process must be accelerated in our hospitals.

Lipodystrophy prevalence rate (13.9%) was fairly high in our study.

The European Group of Pediatric lipodystrophy had reported a prevalence rate of 26% in France, including 7.5% for lipoatrophy, 8.8% for lipohypertrophy and 9.6% for the mixed syndrome in a prospective study covering 477 HIV infected children [12].

Piloya in Uganda found a prevalence rate of 27% of lipodystrophy in 364 HIV infected children [11]. However, Kinabo *et al*. in Tanzania reported lipodystrophy prevalence rate of 30%, including 19% for lipoatrophy, 3.8% for lipohypertrophy and 7.1% for mixed forms in a cross-sectional study on 210 HIV infected children and adolescents aged 1 to 18 years [17].

The prevalence of lipodystrophy therefore varies from one study to another. In all these three researches mentioned above, study design included adolescents aged 18 years in whom the risk of occurrence of lipodystrophy is higher than that of under 15 years [5] [10] [11]. Other diagnostic methods are more accurate and should be used whenever possible; skin fold measurement or muscles Dexa-scan and body fat assessment [18] [19].

In our series, several locations of lipodystrophy were found including 32% in the face, 26% on the lower limbs. Our results are similar to those of Joly in France who found 49% and 48% of locations on the face and lower limbs [13].

Table 3. Factors associated with lipodystrophy.

Associated factors	Number	Lipodystrophy		Odds ratio	P
		Yes N (%)	No N (%)	(IC)	
Age (years)					
≤10	156	15 (9.6)	141 (90.4)	1	
>10	167	30 (18)	137 (82)	0.5 (0.3 - 1)	0.005
Sex					
Female	161	17 (10.6)	144 (89.4)	1	
Male	162	28 (17.3)	134 (82.7)	1 (0.9 - 1.1))	0.042
Clinical stage					
1	2	1 (50)	1 (50)	1	
2	62	3 (4.8)	59 (95.2)	7.5 (5.2 - 9.4)	0.5
3	233	39 (16.7)	194 (83.3)	0.3 (0.2 - 0.8)	0.001
4	26	2 (7.7)	24 (92.3)	2.4 (0.9 - 5.5)	0.06
Treatment duration ARV					
≤60	189	12 (6.3)	177 (93.7)	1	
>60	134	33 (24.6)	101 (75.4)	0.4 (0.2 - 0.7)	<0.001
Initial treatment regimen					
AZT−	145	36 (24.8)	109 (75.2)	1	
AZT+	178	9 (5)	169 (95)	6.3 (0.2 - 8.2)	0.41
D4T−	184	10 (5.4)	174 (94.6)	1	
D4T+	139	35 (25.2)	104 (74.8)	0.2 (0.1 - 0.3)	<0.001
Lopi/rt−	271	33 (12.2)	238 (87.8)	1	
Lopi/rt+	52	12 (23)	40 (77)	0.4 (0.2 - 0.6)	0.06

(AZT−) = Treatment regimen not containing zidovudine; (AZT+) = Treatment regimen containing zidovudine; (D4T−) = Treatment regimen not containing zidovudine; (D4T+) = Treatment regimen containing stavudine; (Lopi/rt−) = Treatment regimen not containing lopinavir/ritonavir; (Lopi/rt+) = Treatment regimen containing lopinavir/ritonavir.

Table 4. Factors associated with the presence of lipoatrophy.

Associated factors	Number	Lipodystrophy		Odds ratio	P
		Yes N (%)	No N (%)	(CI)	
Age (years)					
≤10	156	11 (7)	145 (93)	1	
>10	167	24 (14.4)	143 (85.6)	0.5 (0.3 - 1)	0.004
Sex					
Female	161	8 (5)	153 (95)	1	
Male	162	27 (16.7)	135 (83.3)	0.3 (0.2 - 0.6)	0.0004
Treatment duration (month)					
≤60	189	8 (4.2)	181 (95.8)	1	
>60	134	27 (2)	107 (98)	0.2 (0.1 - 0.3)	<0.001
Initial treatment					
AZT−	145	30 (2)	115 (98)	1	
AZT+	178	5 (2.8)	173 (97.2)	8.6 (5.8 - 9.8)	0.49
D4T−	184	6 (3.3)	178 (96.7)	1	
D4T+	139	29 (2)	110 (98)	0.1 (0.09 - 0.2)	0.01

On the contrary, the European Group of Pediatric Lipodystrophy found that the trunk was the most affected area in 66% of cases, followed by the lower limbs, the face, the upper limbs, the buttocks in 40%; 39%; 37% and 22% of cases respectively [12].

The development of lipodystrophy and especially lipoatrophy may be a source of stigma. Likewise, patients who link lipodystrophy to antiretroviral do not usually adhere to that treatment [12].

Lipoatrophy treatment is not well codified which makes it difficult for patients to get appropriate care. In adults, medical treatment with statines or plastic surgery has provided contradictory results [6] [20]. In our working context, psychological support remains the sole accessible solution. At the time of the survey, the national plan to switch D4T to other less toxic regimens was still underway.

In univariate and multivariate analysis, age above 10 years was significantly associated with lipodystrophy ($P = 0.005$). This result is similar to that found by other authors [10] [12] [17]. Morphological changes therefore increase with age.

Contrary to our study, Aurpibul in Thailand had noticed that lipodystrophy was more common in girls than boys, 61% and 39% of cases respectively [5]. Actually, there are seemed to be gender-based physiological differences in the occurrence of lipodystrophy. At puberty, estrogen and progesterone hormones contribute to fat accumulation in girls whereas in boys, testosterone, an anabolic hormone, maintains little fat accumulation. Thus, lipohypertrophy should normally be expected to be more common in girls than boys. However this was not the case in our study, the frequency of lipoatrophy among boys (16.7%) was higher than that of girls (5%) ($P = 0.004$).

We found no connection between hypercholesterolemia, hypertriglyceridemia, hyperglycemia and the presence of lipodystrophy in children. We think that these biological disturbances were transient and not associated with metabolic syndrome.

Lipodystrophy was found in all antiretroviral therapy regimens in our series. AZT and D4T of Nucleoside Reverse Transcriptase Inhibitors class (NRTIs), historically linked to lipodystrophy, and were used in 20% and 77.8% of our patients with lipodystrophy. Our results are very similar to those of Dollfus *et al*. who found that D4T was used in 92% of patients presenting lipodystrophy compared to 42% for AZT [10].

We found that D4T was significantly associated with the presence of lipodystrophy ($P < 0.001$) and especially lipoatrophy ($P = 0.01$). Our results are similar to those of Viard in France who, in a randomized trial on D4T and risk of lipoatrophy, found 3.6 times higher the risk of developing lipoatrophy when using D4T than AZT [13].

NRTIs particularly thymidinic derivatives (D4T and AZT), have a direct impact on mitochondria. They decrease the mitochondrial DNA and the respiratory chain proteins and increase the production of reactive oxygen. D4T and AZT induce lipolysis and, under certain circumstances, an apoptosis of adipocytes. These molecules interfere with adipocyte differentiation and contribute to activate the production of pro-inflammatory cytokines; while the other NRTIs do not change the rate of the mitochondrial DNA significantly [2].

Proteases inhibitors used in ARV regimen were found in 26.7% of patients presenting with lipodystrophy, this rate is lower than that found by Dollfus *et al*. of 79% [10]. In statistical analysis, there was no link between an exposure to PIs and the development of lipodystrophy ($P = 0.06$). However, some authors found a statistically significant link between exposure to PIs and the occurrence of lipodystrophy [17]. Indeed, protease inhibitors are associated with an alteration of the adipocyt differentiation, an oxidative stress and the production of pro-inflammatory cytokines.

5. Limits for This Study Were

- The method used to diagnosis lipodystrophy (morphological change) might have under estimated the disorder.
- The study was conducted in two hospitals of Ouagadougou and might not represent the profile of all HIV infected children on antiretroviral therapy in Burkina Faso.

6. Conclusion

We found a high prevalence rate of lipodystrophy in HIV-infected children on antiretroviral treatment. Age older than 10 years, WHO clinical stage 3, and long-term exposure to antiretroviral treatment especially D4T were factors most associated with lipoatrophy. Our results highlight the need to make available less toxic antiretroviral drugs for pediatric population. We'll have to try and make health professionals aware of screening for lipodystrophy. More researches on larger cohort in our setting are necessary to determine other metabolic disorders

and associated factors in HIV-infected children treated with antiretroviral.

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