Lipodystrophy syndrome among HIV infected children on highly active antiretroviral therapy in northern India

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Abstract:

Background: It is estimated that about 2.5 million people are living with HIV infection in India. Although antiretroviral drugs have been able to reduce the mortality, these drugs have serious side effects one of which is lipodystrophy syndrome. Most of the drugs used in HAART viz, protease inhibitors, stavudine and nevirapine are associated with lipodystrophy. Hence we conducted this study to assess the prevalence of lipodystrophy in HIV infected children on HAART and its associated risk factors.

Materials and methods: A cross sectional study was conducted on 80 HIV infected children aged 2-18 years of age who were on stavudine based HAART for ≥2 years. These children were assessed for presence of lipodystrophy, its metabolic complications and associated risk factors.

Results: Lipodystrophy was observed in 33.7% of children with lipoatrophy being the commonest subtype followed by lipohypertrophy. Older age, increased duration of treatment and dyslipidaemia were found to be associated in patients with lipodystrophy than those without. On further multivariate analysis of independent risk factors only increased duration of treatment was significantly associated with lipodystrophy. No association was found with insulin resistance.

Conclusion: We observed that lipodystrophy is a common finding in HIV patients treated with HAART for long duration.

Key Words: lipodystrophy syndrome, lipoatrophy, HAART, HIV

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Introduction

HIV infection is increasingly becoming a prominent cause of morbidity and mortality with an estimated 2.5 million people living with HIV in India [(1)]. Antiretroviral drugs have dramatically improved the quality of life and increased the life expectancy but morphological and metabolic complications of the drugs have threatened to short live this achievement. The term Lipodystrophy syndrome was first used to describe morphological complications of these drugs in HIV infected adults. Lipodystrophy syndrome encompasses fat redistribution, defined as fat wasting of extremities/ face or buttocks, fat accumulation in abdomen or dorsocervical spine (buffalo hump) and metabolic complications associated with it- dyslipidaemia, insulin resistance[(2)].

The mechanism responsible for this syndrome remains unclear. It has been proposed that antiretroviral drugs such as protease inhibitors (PI) and/ or nucleoside analogues (stavudine) could contribute to the development of such clinical and metabolic abnormalities [(2, 6, 13-22, 28-35)]. Various risk factors have been found to be associated with the development of lipodystrophy like older age and increasing duration of treatment [(22, 33,34,35)].

Studies have reported complications associated with lipodystrophy syndrome viz cardiovascular complications [(5)] and diabetes mellitus type 2 later in life. The impact of fat redistribution and its associated metabolic complications on HIV infected children is therefore of obvious concern to paediatricians. Various studies have been done worldwide but Indian data is very sparse. Hence we conducted this study to assess the prevalence of fat redistribution and its associated risk factors in our tertiary care centre.

Materials and methods

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A cross sectional study was conducted over a one year period from November 2010 - November 2011 at a tertiary care centre in northern India. Eighty HIV infected children 2-18 years of age who were on Highly Active Antiretroviral Therapy (HAART) for a period of minimum 2 years and who were willing to give an informed consent were included in the study. Those who had serious or life threatening complications of HIV (active tuberculosis, systemic fungal infections, cerebral toxoplasmosis), unwilling to give consent, known diabetic, children on steroids or lipid lowering drugs and those with congenital (SHORT syndrome, Dunnigan syndrome, Kobberling syndrome) or acquired (rheumatoid arthritis, SLE) causes of lipodystrophy were excluded. Approval was taken from the institutional ethical committee. Using the formula for descriptive study ($Z^2 \times p \times q / d^2$) with the estimated prevalence of Fat redistribution in HIV infected patients (p) = 26%, precision error of estimation (d) = 0.10, and alpha = 0.05, a sample size of at least 75 cases was needed to estimate the prevalence

A detailed history including age, sex, duration of treatment, route of transmission was taken. WHO clinical stage and CD4 count [4] at the time of enrolment for HAART were documented from the patient's clinical records. They were examined for signs of fat redistribution according to the criteria mentioned below. Weight and height were measured and BMI calculated. To study the metabolic complications fasting blood samples were collected for lipid profile (serum cholesterol, triglyceride, Low Density Lipoprotein (LDL), Very Low Density Lipoprotein (VLDL) levels), glucose and insulin levels.. HOMA-IR (Homeostasis model assessment of insulin resistance) was calculated as a measure of insulin resistance.

Fat redistribution or lipodystrophy was assessed by physical examination and divided into lipoatrophy, lipohypertrophy and combined subtype. Lipoatrophy was considered when sunken cheeks with prominent zygomatic arch or thin extremities with prominent veins were present with or without buttock atrophy. Lipohypertrophy was considered when increased abdominal girth or fat accumulation 'buffalo hump' was present. They were considered to have fat redistribution if they had one or more signs. One was classed into combined subtype if one had any sign each of lipoatrophy and lipohypertrophy[2].

Dyslipidaemia was defined as the presence of either hypercholestrolaemia (serum cholesterol ≥ 200mg/dl) or high LDL (serum LDL ≥130mg/dl) or hypertriglyceridaemia (serum triglyceride≥150mg/dl). Serum cholesterol, triglyceride and LDL were measured using the enzymatic colorimetric method using Olympus AU400 [2]. Insulin resistance was measured using HOMA-IR which was calculated using the formula HOMA-IR = (fasting glucose (mg/dl) x insulin μU/dl) / 405. Value of greater than 3.1 was considered as insulin resistance [26]. Glucose was measured using GOD-POD method on Olympus AU400. Insulin was measured using ELISA.

Statistical analysis

Statistical analysis was performed by the SPSS program for Windows, version 17.0. Normally distributed data are presented as mean ± SD. Categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis using Shaipro Wilk test. Normally distributed continuous variables were compared using student's t test. The Mann Whitney U test was used for those variables that were not normally distributed. Categorical variables were analyzed using the chi square test. Multivariate Logistic Regression analysis was also used to assess the presence of risk factors with Lipodystrophy. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

Results

A total of 80 HIV infected children with 2 years and more of HAART treatment were recruited. Of these 62 (75.5%) were boys. The mean age of the study population was 10.8 ± 3.39 (3-18 years). The median time since HAART was first initiated was 4.75 ± 1.49 (2-7 years) and all patients were on stavudine based HAART (stavudine, lamivudine and nevirapine). Majority of patients had acquired the infection through vertical transmission (n=68, 85%) followed by blood transfusion (n=7, 8.8%) and intravenous injection (n=5, 6.2%). At the time of initiation of HAART, majority of patients had presented with loose stools (n=26, 32.5%) followed by asymptomatic (n=23, 28.75%), and rest as cough, skin lesions and lymphadenopathy. Majority of patients (n=42, 52.5%) were in stage III at the time of initiation of HAART while (n=25, 31.2%) were in stage I and (n=10, 12.5%) and (n=3, 3.8%) were in stage II and IV respectively.

In our population of 80 children, lipodystrophy was observed in 27 children with a prevalence of 33.7%. All three forms of fat redistribution was observed of which lipoatrophy was commonest (n=18, 66.6%) followed by lipohypertrophy (n=3, 11.1%) and

combined subtype (n=6, 22.2%). As shown in Table1, age and duration of treatment was significantly higher in lipodystrophic group than non lipodystrophic patients.

Table 1.General characteristics and laboratory parameters of patients with and without lipodystrophy.

	Lipodystrophy (n=27) mean±SD / %(n)	Non lipodystrophy(n=53) mean±SD / %(n)	P value
Age	12.48±3.17	9.98±3.157	**0.001***
Sex (Male) male: female	70.37% (19) 19:8	81.1% (43) 43:10	0.27
HAART duration	5.92±0.916	4.264±1.482	**<0.001***
WHO stage I II III IV	 29.6% (8) 22.2% (6) 44.4% (12) 3.7% (1)	 32.1% (17) 7.5% (4) 56.6% (30) 3.8% (2)	 0.306
CD4 count ≥500 not significant 350-499 mild 200-349 advanced ≤199 severe	 48.1% (13) 7.4% (2) 18.5% (5) 25.9% (7)	 35.8% (19) 22.6% (12) 11.3% (6) 30.2% (16)	 0.288 0.090 0.377 0.690
Insulin resistance HOMA-IR≥ 3.1	14.8% (4)	5.7% (6)	0.121
Cholesterol ≥ 200mg/dl	33.3% (9)	5.7% (3)	**0.002****
LDL≥ 130mg/dl	29.6% (8)	9.4% (5)	**0.021****
TG≥150mg/dl	25.9% (7)	5.7% (3)	**0.026****

*p <0.001, **p<0.05

Similarly hypercholesterolaemia, high LDL levels and hypertriglyceridaemia were present in significant number of patients with lipodystrophy than those without. Presence of lipodystrophy did not show any association with insulin resistance, particular gender or WHO clinical stage and immune status of the patient.

To explore further, univariate analysis of the association of risk factors in different subgroups of fat redistribution viz, lipoatrophy, lipohypertrophy and combined subtype were done. As shown in table 2, significant association was found between lipoatrophy and increasing duration of treatment (p value-<0.001) and hypertriglyceridaemia (p value-0.026). Combined subtype was significantly associated with increasing age (p- 0.005), hypercholestrolaemia (p- 0.041) and high LDL levels (p- 0.006). Lipohypertrophy was observed in those with longer duration of treatment but was not statistically significant.

Multivariate analysis was performed to further test the independent effects of variables shown to be univariably associated with the development of fat redistribution. Only increasing duration of treatment (OR = 2.935, 95%CI - 1.576-5.465 (p value- 0.001)) was found to be significantly associated with presence of lipodystrophy.

Table2. Univariate analysis of subgroups of lipodystrophy.

Variable	lipoatrophy (n=18) mean ± SD / % (n)		P value	Lipohypertrophy (n= 3) mean ± SD / % (n)		P value	Combined (n = 6) mean ± SD / % (n)		P value
	Present	Absent		Present	Absent		Present	Absent	
Age	11.94 ± 3.28	10.50 ± 3.34	0.109	11.67 ± 3.21	10.79 ± 3.38	0.661	14.50 ± 2.26	10.53 ± 3.26	**0.005****
Sex (male) M:F	72.2%(13) 2.5:1	79% (49) 3.5:1	0.542	66.7% (2) 2:1	77.9% (60) 3.5:1	0.540	66.7% (4) 2:1	78.4%(58) 4:1	0.413
Duration	5.89± 0.83	4.52 ± 1.55	**<0.001***	6.33 ± 1.15	4.77 ± 1.52	0.082	5.83 ± 1.17	4.74 ± 1.54	0.094
Insulin resistance ≥3.1	33.3% (1)	11.7% (9)	0.334	33.3% (1)	11.7% (9)	0.334	33.3% (2)	10.8% (8)	0.161
Cholesterol ≥ 200mg/dl	27.8% (5)	11.3% (7)	0.085	33.3% (1)	14.3% (11)	0.390	50% (3)	12.2% (9)	**0.041****
LDL ≥ 130mg/dl	22.2% (4)	14.5% (9)	0.475	0%	16.9% (13)	1.000	66.7% (4)	12.2% (9)	**0.006****
TG ≥ 150mg/dl	27.8% (5)	8.1% (5)	**0.026****	0%	13%(10)	1.000	33.3% (2)	10.8% (8)	0.161

LDL- low density lipoprotein, TG- triglyceride level, M-male, F- female

*p<0.001, ** p<0.05

Discussion

The introduction of HAART as the treatment strategy for HIV has improved the life span of these patients but at the cost of certain fat redistribution abnormalities and its metabolic complications. The long term concern raised by these abnormalities includes cardiovascular complications and diabetes mellitus later in life [5] and also decreasing adherence to therapy [24]. Out of the various antiretroviral drugs used protease inhibitors (PI) especially indinavir has been extensively studied as the cause of lipodystrophy. The focus is now shifting towards nucleoside reverse transcriptase inhibitors (NRTI) and non nucleoside reverse transcriptase inhibitors (NNRTI) especially stavudine and nevirapine respectively as these drugs are commonly used in developing countries [6, 9, 10]. Unlike in developed countries where patients receive PI based regimens, our patients were treated with stavudine, lamivudine and nevirapine. Since these changes start appearing within 1 year of treatment and become more apparent in the 2nd year of treatment [8, 10] hence we included those patients who were on treatment for more than 2 years.

Most of the published studies have patients treated with PI based HAART and has reported 1-43% prevalence of lipodystrophy [2, 3, 6, 13-20]. Our study is one of those very few studies conducted on stavudine based HAART especially in pediatric age group. In our study lipodystrophy was observed in 33.7%. Few studies on stavudine based HAART have reported a prevalence between 27% - 60.7 %[8, 22, 28, 29, 30, 33-34]. We found lipoatrophy as the commonest subtype similar to others [8, 11, 12, 20, 21, 33, 34] whereas Aurpibul et al [22] reported lipohypertrophy as the commonest subtype.

In our study lipodystrophy was significantly associated with older age group and increasing duration of treatment. However on multivariate analysis significant association was observed only with increasing duration of treatment. This was similar to what was reported by Aurpibul et al[22], Kinabo et al[33], Piloya et al[34], Innes et al[35] and Griensven et al whereas Pujari et al[8] did not find any association with age and duration of therapy.

We did not observe significant association of lipodystrophy with CD4 counts, female sex as reported by Aurpibul et al [22]. In our experience there was significant difference between the lipodystrophy group and non lipodystrophy group with regard to hypertriglyceridaemia, hypercholestrolaemia and high LDL levels and is consistent with that reported by Pujari et al[8], Musiime et al[32] and Aurpibul et al[22]. Piyola et al[35] did not observe any significant difference between the two groups with regard to presence of dyslipidaemia. Dyslipidaemia was also observed in non lipodystrophic group which is similar to findings of Piyola et al[34] and suggest that lipid metabolism abnormalities could precede clinical lipodystrophy. We did not observe any association of lipodystrophy with insulin resistance.

NRTIs lead to development of lipodystrophy by

acting on mitochondrial DNA polymerase enzyme and leading to mtDNA depletion. Role of mitochondria in adipocytes appear to be more complex and is directed towards providing energy for triglyceride synthesis and storage. Mitochondrial dysfunction in adipocytes limits lipogenesis and lipolysis, and directs metabolism towards oxidation while increasing basal glucose uptake. Hence the clinical presentation of fat wasting and absence of dyslipidaemia and insulin resistance with NRTI based HAART [23]. Despite this fact we observed that on univariate analysis, lipoatrophy was significantly associated with hypertriglyceridaemia. This was similar to observation by Saint Marc et al [11] and Pujari et al [8]. In our experience few patients also developed mixed type of lipodystrophy which was associated with increasing age, hypercholestrolaemia and high LDL. Our finding is in sync with the existing literature which states that mixed type is more observed in adolescents and it follows a gradual and progressive course and in some patients lipoatrophy preceeds lipoaccumulation and is associated with lipid abnormalities like hypercholestrolaemia and hypertriglyceridaemia[27].

The limitation of this study was the cross section study design and limited sample size. Regional analysis of body fat composition by various techniques like DEXA[31, 35], bioelectric impedence[25] and measurement of skin fold thickness[32] are more sensitive methods. Due to limitation of resources, subjective method was used to assess fat redistribution. In out tertiary centre, HAART with stavudine, lamivudine and nevaripine is used as the first line of treatment. However both stavudine and nevirapine individually are known to cause lipodystrophy so we could not say clearly which of the drugs was responsible for lipodystrophy in our study. Further studies are needed to study the individual effects of these drugs.

Conclusion

Lipodystrophy was observed in 33.7% of the study group with lipoatrophy as the commonest subtype. Lipodystrophy was significantly associated with increasing duration of treatment. However, no association was found with either gender, WHO clinical stage, immune status and insulin resistance. On subgroup analysis lipoatrophy was significantly associated with increasing duration of treatment and hypertriglyceridaemia. We conclude that lipodystrophy is a common finding in HIV infected children on HAART. With increased life span thus increasing the duration of treatment, the prevalence of lipodystrophy will increase in future. Regular assessment of these children for lipodystrophy is a must for early corrective measures. .

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