

LIPODYSTROPHY SYNDROME IN HIV-INFECTED CHILDREN ON HAART

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Lipodystrophy syndrome (LD) is common in HIV-infected children, particularly those taking didanosine, stavudine or zidovudine. Lipo-atrophy in particular causes major stigmatisation and interferes with adherence. In addition, LD may have significant long-term health consequences, particularly cardiovascular. Since the stigmatising fat distribution changes of LD are largely permanent, the focus of management remains on early detection and arresting progression. Practical guidelines for surveillance and avoidance of LD in routine clinical practice are presented. The diagnosis of LD is described and therapeutic options are reviewed. The most important therapeutic intervention is to switch the most likely offending antiretroviral to a non-LD-inducing agent as soon as LD is recognised. Typically, when lipo-atrophy or lipohypertrophy is diagnosed the thymidine nucleoside reverse transcriptase inhibitor (NRTI) is switched to a non-thymidine agent such as abacavir (or tenofovir in adults). Where dyslipidaemia is predominant, a dietician review is helpful, and the clinician may consider switching to a protease inhibitor-sparing regimen or to atazanavir.

Antiretroviral agents have led to dramatic advancements in life expectancy and quality of life for people living with HIV/AIDS. Despite this progress, lower-income countries are forced to use older, less expensive antiretrovirals such as stavudine, which are associated with a relatively high frequency of late toxic effects. Nevertheless, the older antiretrovirals are likely to remain the backbone of the national first-line highly active antiretroviral therapy (HAART) regimen in South Africa for the foreseeable future due to cost constraints.^{1,2} One of the more common late toxic effects of older antiretrovirals is lipodystrophy syndrome (LD).

LD is an umbrella term referring to peripheral lipo-atrophy (LA), central lipohypertrophy (LH), and dyslipidaemia associated with insulin resistance.^{3,4} These may occur alone or in combination. Although LD was initially thought to be a syndrome of fat redistribution resulting in peripheral LA combined with central LH, preliminary data from the FRAM study in adults (Study of Fat Redistribution and Metabolic Change in HIV infection)⁵ indicate that LH and LA are less closely linked than was previously presumed. Other authors have also noted that LH and LA often occur independently of one another.⁶ In addition, dyslipidaemia associated with HAART may occur in the absence of LA or LH.⁷

LA results in disfigurement, particularly of the face (Figs 1 – 6), which can lead to stigmatisation and even forced

disclosure of HIV status. This disfigurement has a major impact on adherence, particularly in adolescents.^{3,6,7} In addition, the long-term health consequences of LD in HIV-infected children, who require lifetime antiretrovirals, are considerable: the most important consequence arises from dyslipidaemia and insulin resistance, which are known to significantly accelerate lifetime risk for cardiovascular disease in HIV-infected adults with LD.⁸ It is unclear whether transient drug-induced dyslipidaemia in childhood increases the lifetime risk of cardiovascular disease in children.^{9,10} Nonetheless, these negative health outcomes are of concern given that the prevalence of HAART-related LD in resource-limited settings may be as high as 47% after 2 years of therapy.⁶

The mechanisms of LD have not yet been firmly established. The mechanism of LA is related to mitochondrial damage, particularly in adipocytes.¹¹ HAART-related apoptosis of adipocytes and suppression of pre-adipocyte differentiation have been described in protease inhibitor (PI)-induced LA.¹² A similar mechanism may occur in nucleoside reverse transcriptase inhibitor (NRTI)-induced LD, since it is known that NRTIs such as stavudine can damage adipocyte mitochondria¹¹ and cause a reduction in functioning mitochondria in adults.¹³ Other chronic toxic effects such as lactic acidosis and peripheral neuropathy have also been associated with mitochondrial dysfunction.^{14,15} It has been suggested

that unknown agents released from damaged mitochondria in adipocytes may directly trigger apoptosis which leads to subcutaneous fat loss. Quantification of mitochondrial DNA in peripheral leucocytes may be an early warning sign of impending LD in patients exposed to antiretrovirals.^{16,17} Circulating growth hormone (GH) levels are significantly reduced in patients with LA/LH, and this is likely to aggravate the abnormal fat distribution.¹⁸

HAART-related dyslipidaemia is thought to be mediated by a different, though related, mechanism: PI-induced alterations in adipokines and pro-inflammatory cytokines cause an increased production of triglycerides and cholesterol in hepatocytes, while simultaneously inhibiting glucose uptake in peripheral adipocytes.¹⁹

RISK FACTORS

The risk of developing LD is strongly related to the dosage and duration of exposure to antiretroviral agents. The thymidine NRTIs (zidovudine and stavudine) and didanosine have been linked to LA/LH.^{20,21} In comparison, abacavir, tenofovir, and lamivudine have minimal or no LA/LH-causing effect.²² Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are considered a less potent cause of LA.⁷ Although efavirenz has been associated with lipomastia in some children, this usually resolves spontaneously without withdrawal of efavirenz.^{23,24} PIs have been linked to dyslipidaemia,²⁵ and less strongly to LA/LH.^{21,26}

Stavudine, in particular, has been found to be a potent cause of LA in children when taken in the standard paediatric dose of 1 mg/kg/dose twice daily.^{3,7,27,28} Owing to the long-term toxicity of this dose, stavudine is now rarely used in the developed world. A review by Hill *et al.*²⁹ has recently led the World Health Organization (WHO) to recommend a reduction in the standardised dose of stavudine for adults weighing over 60 kg from 40 mg to 30 mg twice daily,³⁰ since it has been shown that a reduced dose results in a markedly lower risk of LD, while maintaining excellent antiviral efficacy.^{31,32}

The recommended dose of stavudine for children, however, has not yet been reduced. Since the dose of stavudine is a major risk factor for the development of LD,³³ it would be reasonable to expect that the incidence of LD will fall when a lower dose is employed. The current standard paediatric dose of stavudine (1 mg/kg/dose twice daily) was extrapolated from the pharmacokinetic parameters of the adult dose of 40 mg twice daily, using data from a few small but well-controlled paediatric pharmacokinetic studies³⁴⁻³⁶ which showed that an oral dose of 1 mg/kg/dose twice daily in children under 12 years results in plasma exposure similar to that of adults taking 40 mg twice daily, and that an oral dose of 0.5 mg/kg/dose twice daily in children

Significance of lipodystrophy syndrome

- Lipodystrophy syndrome (LD) is common in HIV-infected children, particularly in those taking didanosine, stavudine or zidovudine.
- Lipo-atrophy (LA) (a component of LD) causes major stigmatisation and interferes with adherence.
- LD may have significant long-term health consequences, particularly cardiovascular.
- LA is largely permanent, so the focus remains on early detection and arresting progression.

What to look out for

- Look for a lean, muscular appearance of face and limbs with prominent limb veins due to loss of subcutaneous fat tissue.
- Compare the child's tricep and bicep skin-fold thickness with your own as a rough guide.
- Shrinking buttocks with or without an enlarging abdomen may be monitored using a waist-to-hip ratio (WHR).
- Children on HAART should have their blood lipids measured routinely every year.

What to do

Where subcutaneous LA or lipohypertrophy is diagnosed:

- The most likely offending NRTI should be switched to abacavir (or tenofovir in adults).

Where dyslipidaemia is predominant:

- A dietician review is helpful.
- Consider switching to a PI-sparing regimen or to atazanavir.
- Look for insulin resistance.
- Statins and metformin are only used in extreme cases.

results in plasma exposure similar to that of adults taking 20 mg twice daily.

Particular mitochondrial DNA sub-groups (haplogroups) have been associated with a vulnerability to developing LA after exposure to HAART.³⁷ A recent study showed that Caucasian American men on HAART who have the H mitochondrial haplogroup were at significantly increased risk of LA.³⁷ In addition, certain mitochondrial DNA mutations may make an individual more vulnerable to developing LD when exposed to antiretroviral agents. This may occur because variations of mitochondrial DNA in adipocytes may reduce the efficiency of energy production or lead to increased oxygen free-radical production, resulting in a reduced mitochondrial reserve and an increased vulnerability to apoptosis when exposed to mitochondrial toxins such as antiretrovirals.

DIAGNOSIS

A complex set of diagnostic criteria for the diagnosis of LD has been developed for adults by Carr *et al.*³⁸ Equivalent diagnostic criteria for children have not been formally defined. Most clinicians employ a combination of objective anthropometric and biochemical measurements and a subjective assessment in order to diagnose LD in children.^{6,7,33,39,40} Physical signs in children are due to loss of subcutaneous fat in limbs, buttocks and face, with or without accumulation of intra-abdominal visceral fat. Loss of limb fat results in prominent limb veins and a well-defined, muscular appearance of limbs in the presence of a normal or enlarged abdomen. Reduced skin-fold thickness (SFT) may be subjectively assessed by comparing it with one's own SFT as a rough guide.

Loss of buttock fat, with or without enlargement of the abdomen, results in a greatly increased waist-to-hip ratio (WHR). Breast enlargement and buffalo hump may occur after puberty. Other useful anthropometric measurements include mid-upper arm circumference (MUAC) and waist circumference, from which the waist-to-MUAC ratio can be calculated. SFT measurements may be used to calculate the torso-to-arm ratio (TAR) as follows: $TAR = \frac{[\text{subscapular} + \text{suprailiac SKF}]}{[\text{bicep} + \text{tricep SFT}]}$. A TAR z-score of >2.0 has been used as a diagnostic criterion in some studies.³⁹

As HAART-related dyslipidaemia may occur independently of LA/LH,⁵⁻⁷ children on HAART should have their blood lipids measured routinely at least once a year.

Facial fat loss is often subtle and difficult to detect unless severe. The facial muscles are not normally noticeable because they are covered in fat. Loss of facial fat results in a lean, muscular appearance of the face with deep laugh-lines when smiling. An old photograph may be helpful. Figs 1 and 2 show a child with mild LA of the face. Some recovery is seen 4 years after changing from a stavudine-containing regimen (Fig. 3). Fig. 4 shows a child with moderate facial LA. Figs 5 and 6 show a child with severe facial LA. Her LA was already advanced when she was changed from a stavudine-containing regimen 4 years previously, and is unlikely to improve.

To date there are limited data comparing the sensitivity and specificity of anthropometric and biochemical diagnostic criteria against a gold standard such as dual-energy X-ray absorptiometry or magnetic resonance imaging to diagnose early LA/LH in HIV-infected children. Studies are underway to define a practical set of diagnostic criteria to detect early LD in children in resource-limited settings. Since at least 30% of peripheral fat must be lost before LA becomes visibly evident,⁴¹ it is hoped that some combination of anthropo-

metric and biochemical measures will have reasonable sensitivity and specificity to detect LA/LH in children before it causes noticeable disfigurement (S Innes *et al.* – unpublished data). This will be an important contribution to paediatric HIV care in the developing world.



Fig. 1. Mild LA of the face, front view.



Fig. 2. Mild LA of the face, side view.



Fig. 3. The same child as in Fig. 1. Some recovery is seen 4 years after withdrawal of stavudine.

MANAGEMENT

Since the disfigurement caused by LD is largely permanent, the focus of management is on early detection and arrest of progression. Once identified, the most likely offending drug is usually withdrawn in an attempt to prevent progression, and is replaced by a less LD-inducing antiretroviral. Where dyslipidaemia is identified, diet and lifestyle modification are essential. If severe and persistent (total cholesterol >13 mmol/l or triglycerides >8.5 mmol/l),¹ the PI may be switched to a PI-sparing agent or changed to atazanavir/ritonavir (ATV/r), which has less effect on blood lipids.²¹ The effect of statins in lowering triglycerides and cholesterol is well established;⁴² however, statins are only licensed for use in children over 12 years of age. The potential interaction of statins with PIs must be borne in mind. Metformin has been shown to be effective for LD-related insulin resistance in adults⁴³ and for obesity-related insulin resistance in HIV-uninfected children.⁴⁴ However, metformin is rarely used in LD-related insulin resistance in children.

When LA/LH is diagnosed, significant benefit in halting progression has been shown from switching the thymidine NRTI to a non-thymidine agent such as abacavir.²¹ Tenofovir is generally avoided in children because of renal toxicity and osteopenia. However, there may be a place for switching to tenofovir in older children.⁴⁵ This switch typically arrests progression of LA/LH, and may result in a small degree of reversal if LA is caught early. Various authors have demonstrated that the more advanced the LA, the less likely it is to reverse when the offending drug is removed.^{46,47} Intra-dermal injections of a biodegradable filler such as poly-L-lactic acid (Sculptra) can ameliorate the aesthetic effect of facial LA in adults,⁴⁸ but this treatment is not appropriate for children. In addition, the cost is significant and the effect is not permanent and injections may need to be repeated. Uridine (NucleomaxX) partially reverses the mitochondrial toxicity caused by thymidine NRTIs, and may have a small but beneficial effect on disfiguring LA. Uridine is not currently available in South Africa, and it has no effect on dyslipidaemia.⁴⁹ Growth hormone-releasing hormone analogues (GH-RH) are helpful in the treatment of LA/LH.⁵⁰ The mechanism probably involves reversing the reduced GH levels that are consistently found in patients with LA/LH. Although the side-effect profile of GH-RH therapy is attractive, the cost is prohibitive. Future treatments may involve adipokines such as leptin, but these remain experimental.²¹

CONCLUSION

Research into reducing the paediatric dose of stavudine is urgently needed in order to minimise the risk of LD without compromising antiviral efficacy, since the number of at-risk HIV-infected children exposed



Fig. 4. Moderate LA of the face, front view. Note the loss of the buccal fat pad, resulting in lean, muscular appearance of the face with deep laugh-lines.



Fig. 5. Severe LA of the face, front view. This patient's LA was already advanced when she was changed from a stavudine-containing regimen 4 years previously. Her LA is unlikely to improve.



Fig. 6. Severe LA of the face, side view.

to long-term stavudine therapy in South Africa is very large. In addition, non-thymidine NRTIs such as abacavir and tenofovir should be more widely available, particularly in the public sector.

Further research is needed to isolate the particular mitochondrial mutations that make a child vulnerable to LD. This may help public sector clinicians to predict which children should avoid thymidine NRTIs and rather be started on a more expensive, less LD-inducing antiretroviral regimen.

Finally, since effective treatment of LD is difficult and remains beyond the reach of resource-limited rural communities, early detection is paramount. It is essential to define a simple set of diagnostic criteria to identify early LD in children that can be easily implemented in resource-limited settings. This will allow the progression of LD to be halted before it causes noticeable disfigurement and stigmatisation. Children should be switched from stavudine (or zidovudine) to abacavir (and adults to tenofovir or abacavir) at the slightest sign of LD.

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