Mitochondrial toxicities of nucleoside analogue reverse transcriptase inhibitors in AIDS cases

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Abstract

The development of antiretroviral therapy (ART) has been one of the most dramatic progressions in the history of medicine. Concomitant with this momentous therapeutic advance, the mitochondrial toxicities of ART were recognized as an important clinical entity. Aim: The aim was to study the mitochondrial toxicities in terms of peripheral neuropathy (PN), lipodystrophy (LD), hepatic steatosis, lactic academia (LA), and pancreatitis developing in AIDS cases on nucleoside analog reverse transcriptase inhibitors (NRTIs) based ART regimens. Materials and Methods: An observational study, which included 90 AIDS cases, receiving first line ART regimens containing two NRTIs (zidovudine [AZT]/stavudine [d4T] with lamivudine [3TC]) and one nonNRTIs (nevirapine/efavirenz) was conducted at Skin-VD outpatient department of a tertiary care hospital attached to a Medical College. Thorough history was taken, and clinical examination was done. Cases were subjected to measurements of abdominal girth and mid-arm circumference, liver function tests, blood sugar, lipid profile, serum lactate, and amylase levels. Results: Of 90 cases on ART, 66% were males and 34% were females. Mitochondrial toxicities developed in 26 (30%) cases out of 90, which included 3 (7%) out of 42 cases on AZT + 3TC and 23 (48%) out of 48 cases on d4T + 3TC. Most common toxicity was PN seen in 20 (22%) cases; male cases developed PN at a lower CD4 count than female cases. LD was observed in total of 13 (14.5%) cases; deposition of fat in the abdomen in seven cases and at the nape of the neck (buffalo hump) in one case while loss of fat from extremities was seen in seven cases and loss of buccal fat in seven cases. Women presented more with fat accumulation (breast and abdomen), while men with loss of fat (limbs and buttocks). Both PN and LD were more common in d4T based regimen. LA was reported in one case on d4T. Hepatic steatosis was seen in three cases and pancreatitis in one case receiving AZT. Conclusion: Regular monitoring and early diagnosis of mitochondrial toxicities with timely switch to safer alternatives is of utmost importance.

Key words: Lipodystrophy, mitochondrial toxicities, nucleoside analogue reverse transcriptase inhibitors, peripheral neuropathy

INTRODUCTION

The development of antiretroviral therapy (ART) has been one of the most dramatic progressions in the history of medicine. With the availability of free ART through government run ART centers human immunodeficiency virus (HIV) related morbidity and mortality have declined significantly. ART includes nucleoside analog reverse transcriptase inhibitors (NRTIs), such as zidovudine (AZT), which was the first antiretroviral drug approved by the US FDA for management of HIV in 1987 has revolutionized the management of HIV in combination with other agents–by converting AIDS from being a lethal illness to a chronic, manageable disease. Nucleoside analogues that inhibit reverse
Mitochondrial toxicities of NRTIs

Transcriptase remain a cornerstone of ART for HIV infection. These agents inhibit HIV replication but can also inhibit the human DNA polymerase γ and thereby replication of mitochondrial DNA, leading to depletion of mitochondrial DNA and drug toxicity. The spectrum of mitochondrial toxicities include peripheral neuropathy (PN), hepatic steatosis, lactic academia (LA), pancreatitis, myopathy, cardiomyopathy, and proximal renal tubular dysfunction.

Aims

To study the mitochondrial toxicities in terms of PN, LD, hepatic steatosis, LA, and pancreatitis developing in AIDS cases on NRTI based ART regimens (AZT/stavudine [d4T] + lamivudine [3TC]).

Materials and Methods

An observational study, which included 90 AIDS cases receiving first line ART regimens containing two NRTIs (AZT/d4T with 3TC) and one nonNRTIs (nevirapine [NVP]/efavirenz [EFV]) attending Skin-VD outpatient department of a tertiary care hospital attached to a Medical College, was conducted. Thorough history was taken and clinical examination was done. Cases were subjected to measurements of abdominal girth and mid-arm circumference, liver function tests, blood sugar (fasting and postprandial), serum lipid profile, serum lactate and amylase levels (when indicated) and ultrasonography abdomen.

Results

Of 90 cases on ART, 66% were males and 34% were females. AZT + 3TC + NVP/EFV regimen started in 42 (47%) cases and d4T + 3TC + NVP/EFV in 48 (53%) cases [Table 1]. Median CD4 count at initiation of ART was 111 cells/cc. Mitochondrial toxicity developed in 26 (30%) cases out of 90 which included 3 (7%) out of 42 cases on AZT + 3TC and 23 (48%) out of 48 cases on d4T + 3TC [Figure 1]. Most common ADR was PN seen in 20 (22%) cases; male cases developed PN at a lower CD4 count than female cases [Tables 2 and 3]. Lipodystrophy (LD) was observed in total of 13 (14.5%) cases; deposition of fat in the abdomen in seven cases and at the nape of the neck (buffalo hump) in one case, while loss of fat from extremities was seen in seven cases and loss of buccal fat in seven cases [Table 4]. Women presented more with fat accumulation (breast and abdomen) while men with loss of fat (limbs and buttocks). Both PN and LD were more common in d4T based regimen. LA was reported in one case on d4T. Hepatic steatosis was seen in three cases and pancreatitis in one case receiving AZT. Five cases on d4T were shifted to AZT due to toxicities; though

Table 1: Sex and regimen-wise distribution of cases

|                  | AZT+3TC | d4T+3TC | Total |
|------------------|---------|---------|-------|
| **Males**        |         |         |       |
| Cases on AZT+3TC | 28      | 30      | 58    |
| Cases on d4T+3TC | 14      | 18      | 32    |
| **Total**        | 42      | 48      | 90    |

AZT=Zidovudine, 3TC=Lamivudine, d4T=Stavudine

Table 2: Various mitochondrial toxicities (n=90)

| Mitochondrial toxicities | AZT+3TC (n=42) | d4T+3TC (n=48) | Total (n=90) (%) |
|--------------------------|----------------|----------------|------------------|
| PN                       | -              | 01             | 12 (22)          |
| LD                       | -              | 02             | 09 (14.5)        |
| Hepatic steatosis        | 01             | 02             | 09 (14.5)        |
| LA                       | -              | 01             | 01 (1.1)         |
| Pancreatitis             | -              | 01             | 01 (1.1)         |

AZT=Zidovudine, 3TC=Lamivudine, d4T=Stavudine, PN=Peripheral neuropathy, LD=Lipodystrophy; LA=Lactic academia

Table 3: Peripheral neuropathy in relation to CD4 count

|                  | AZT+3TC (n=42) | d4T+3TC (n=48) | Median CD4 count (cells/mm$^3$) |
|------------------|----------------|----------------|-------------------------------|
| Male             | -              | 12             | 69                            |
| Female           | 01             | 07             | 144                           |
| **Total**        | 01             | 19             | 20                            |

AZT=Zidovudine, 3TC=Lamivudine, d4T=Stavudine

Table 4: Pattern of LD (n=13)

| Patterns of LD | AZT+3TC (n=42) | d4T+3TC (n=48) | Total |
|----------------|----------------|----------------|-------|
| Fat deposition |                |                |       |
| Abdomen        | -              | 05             | 02    |
| Nape of neck   | -              | -              | 01    |
| Loss of fat    |                |                |       |
| Extremities    | -              | 02             | 03    |
| Buccal pad     | -              | 06             | 01    |

AZT=Zidovudine, 3TC=Lamivudine, d4T=Stavudine, LD=Lipodystrophy

Figure 1: Number of cases on zidovudine (n = 42) and stavudine (n = 48) developing mitochondrial toxicities
tenofovir could have been an ideal switch, but was not available [Table 5].

**A few interesting cases of mitochondrial toxicities**

A 12-year-old male with baseline CD4 count 392 cells/mm³ who was started on AZT + 3TC + NVP; presented after 10 months of regular ART with complaints of severe abdominal pain and vomiting. Serum amylase was 1140 IU/L, blood urea - 37 mg, serum creatinine - 0.8, and CT abdomen was suggestive of pancreatic necrosis. This was suggestive of acute pancreatitis due to ART, that could have been due to 3TC. 3TC induced pancreatitis is rare in adults; although the incidence varied in pediatric patients from 8% to 38%.[4] Pancreatitis is one of the most serious mitochondrial toxicity and requires immediate management.

A 40-year-old female with recurrent herpes zoster and pulmonary Koch’s with baseline CD4 count 317 cells/mm³, was put on d4T + 3TC + NVP; presented after 1 year of regular ART with the complaints of nausea, vomiting, and breathlessness for 3-4 weeks. On examination, there was a loss of fat from the extremities and increase in abdominal fat. Her plasma lactate was 5.4 mmol/L, triglyceride - 405 mg/dl, very low-density lipoprotein - 81 mg/dl, and liver function test were normal. This was thus suggestive of d4T-induced LD syndrome.

As symptoms of LA are subtle; high index of suspicion is required for early diagnosis before progression to outcome.

**Table 5: Alternate regimen in cases with sever ADR (n=5)**

| Number of cases | Basic regimen | Changed regimen | Reason |
|-----------------|---------------|-----------------|--------|
| 03              | d4T+3TC+NVP   | AZT+3TC+NVP     | LD     |
| 01              | d4T+3TC+NVP   | AZT+3TC+NVP     | LD+PN  |
| 01              | d4T+3TC+NVP   | AZT+3TC+NVP     | LA     |

ADR=Adverse drug reactions, d4T=Stavudine, 3TC=Lamivudine, NVP=Nevirapine, AZT=Zidovudine, LD=Lipodystrophy, PN=Peripheral neuropathy, LA=Lactic academia

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Figure 2: Buffalo hump due to stavudine

Figure 3: Loss of buccal pad of fat due to stavudine

Figure 4: Central fat accumulation and peripheral lipoatrophy due to stavudine

Figure 5: Zidovudine induced peripheral lipoatrophy
DISCUSSION

In a study by Hforett-Smith, d4T-induced PN and LD were found in 24% and 16% cases respectively[6] while Saint-Marc et al. reported LD in 63% cases on d4T, and in 18.75% patients taking AZT after a median time of 14 months; the relative risk of developing fat wasting was 1.95 in the d4T group compared to AZT group (95% confidence interval).[6] In the present study d4T-induced PN and LD were found in 40% and 23% cases and AZT induced PN and LD in 2.4% and 4.8% cases respectively. LD syndrome may be attributed to mitochondrial toxicity of NRTIs after 12-18 months of therapy.[7] Main clinical features are peripheral fat loss (buccal pad and extremities) and central fat accumulation within the abdomen (crix belly or prostate paunch), breasts (gynaecomastia) and over the dorsocervical spine (buffalo hump) and other peripheral lipomatosis [Figures 2-5]. The metabolic features of the syndrome include hypertriglyceridemia, hypercholesterolemia, insulin resistance, type two diabetes mellitus/impaired glucose tolerance and LA.[11,12] PN is the primary dose-limiting toxicity of Stavudine with symptoms similar to neuropathy associated with didanosine (ddl) and zalcitabine. The incidence of PN is dose related. Symptomatic patients develop tingling, burning and pain in the lower extremities, especially at night. It usually resolves within 1-9 weeks of discontinuation of stavudine therapy.[6] Ananworanich et al. have reported reversal of mitochondrial toxicities after switching from d4T/ddI to tenofovir/3TC regimen.[9] Van Griensven et al. found tenofovir/abacavir significantly superior to AZT for recovery from lipodystrophy due to d4T.[10] Saint-Marc et al. found that 5 out of 12 patients had a major or mild improvement in their LD after stavudine was discontinued.[6]

CONCLUSION

Mitochondrial complications are a challenging issue because of potential of morbidity, mortality and distressing morphologic disfigurement. The most common cause culprit was stavudine, which is still used as part of free ART program in resource restricted setup. The latest WHO guidelines recommend replacing stavudine with tenofovir or AZT in first-line ART in resource-limited settings. There are many issues remaining to be clarified about the effects of NRTIs on mitochondria and the potential for clinical manifestations of these effects. Some of these issues involve the differing adverse effects among NRTIs, which may be associated with mitochondrial toxicities, different NRTIs have been reported to have varying magnitude of inhibitory effect on gamma polymerase in vitro, there may be differences among NRTIs regarding the ability of gamma polymerase to proofread and excise the NRTI once it has been incorporated into the DNA chain and finally, it is not understood why only some patients appear to have mitochondrial toxicity or clinical manifestations of such toxicities. Regular monitoring and early diagnosis of mitochondrial toxicities with timely switch to safer alternatives (nucleotide reverse transcriptase inhibitor/tenofovir based) is of utmost importance.

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