

Myopathies Secondary to Anti-Retroviral Therapy in Human Immunodeficiency Virus Positive Patients: A Review

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Abstract

Antiretroviral therapy has changed human immunodeficiency virus (HIV) infection and increased the life expectancy of such patients. More patients are taking antiretroviral drugs (ARTs) for longer periods of time. Zidovudine (ZDV), a nucleoside reverse transcriptase inhibitor is known to cause mitochondrial toxicity and leads to various side effects including myopathy. Mitochondrial toxicity can be fatal and is treated by supportive care and discontinuing NRTIs. Withdrawal of offending drug along with metabolic cofactors like thiamine, carnitine, and riboflavin may be helpful in managing mitochondrial toxicity. Clinicians should be able to recognize effects of chronic toxicity of ARTs, especially mitochondrial toxicity leading to myopathy.

Keywords: Antiretroviral; Mitochondrial toxicity; NRTI; Overdose; Myopathy; ZDV; Zidovudine

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Introduction

Neurological complications are commonly seen in patients with HIV infection. Myopathy is one of the neurological manifestations of HIV which can be caused by complication of HIV itself or may also result from the medicines used to control HIV. Symptomatic primary muscle disease is rare in patients with HIV infection. Muscle involvement in HIV infection varies from asymptomatic muscle enzyme elevation to severe, HIV-associated polymyositis or pyomyositis. Drug-induced myopathy is among the most common causes of muscle disease. Initially anti retroviral therapy (ART) associated myopathy was described with Zidovudine (ZDV). Nucleoside reverse transcriptase inhibitors (NRTIs) were found to cause myopathy that clinically resembles idiopathic PM and HIV myopathy [1]. NRTI myopathy was more common in the past when ZDV, in particular, was used at higher doses [2]. ZDV has been marked with a black box warning for prolonged use due to its association with myopathy. Mitochondrial toxicity is a major adverse effect of nucleoside analogue treatment and can lead to myopathy.

Pathogenesis

Nucleoside analogues inhibit viral DNA polymerase (reverse

transcriptase) and thus inhibit HIV replication [3]. However, NRTIs can also bind to other human DNA-polymerases, like DNA polymerase beta and mitochondrial DNA polymerase gamma (responsible for the replication of mitochondrial DNA). Inhibition of mitochondrial DNA enzyme polymerase-gamma leads to depletion of mitochondrial DNA and impairment of oxidative phosphorylation [4]. On accumulation of dysfunctional mitochondrial protein, the mitochondria are unable to perform metabolic functions, such as oxidation of fatty acid and oxidative phosphorylation. Disruption of oxidative phosphorylation results in increased production of reactive oxygen species.

A disruption of oxidative phosphorylation leads to energy loss (decreased ATP) [5], reactive oxygen species, damage proteins, lipids, and mitochondrial DNA. NRTIs can also influence intracellular nucleoside transporters, disturbing the balance of the intracellular nucleoside pools or alter kinetics of phosphorylation of natural nucleoside [6]. Due to mitochondrial dysfunction, the metabolism of pyruvate is shifted to lactate, with a decrease in energy production.

Epidemiology

The incidence of ZDV induced myopathy is not known. However,

some studies are available as per literature search. Sagar et al [7] in their study of 147 HIV patients on ZDV for a period varying from 1-7 years did not find that any symptoms or objective muscle weakness and 10.8% of cases had marginally raised serum CK levels. However, all muscle biopsies were normal on light microscopy.

In a study of HIV patients on ZDV by Peters et al., clinical and biochemical evidence of proximal myopathy was seen in 7 of 88 patients (7.9%). The duration of ZDV use was more than 270 days for 41 out of 88 patients and all the 7 patients with myopathy belonged to this subgroup (17%). In this study, four out of these seven patients had histological evidence of myopathy on light microscopy [8]. Studies have shown the incidence of myopathy ranging from 8 to 50% based on clinical, biochemical or histopathological criteria [8, 9].

Myopathy Associated with ARTs

Nucleoside reverse transcriptase inhibitors (NRTIs) associated myopathy

NRTIs associated myopathy was more common in the past when ZDV (first described, and resemble Polymyositis and HIV myopathy), in particular, was used at higher doses than the currently administered dosage [10-13].

Toxic mitochondrial myopathies related to other nucleoside analog reverse transcriptase inhibitors and newer HAART

Simpson et al [14], in case series involving 69 patients studying the HIV-associated neuromuscular syndrome observed myopathy in 2 patients not on ZDV therapy (but were on stavudine, didanosine and efavirenz).

Indinavir, lamivudine, ritonavir, saquinavir, stavudine and Zalcitabine are uncommonly associated with myalgia or myopathy [15-17].

Tenofovir, abacavir and emtricitabine appear to be weaker inhibitors of mitochondrial function than ZDV and have not been associated with myopathy [18].

Raltegravir associated myopathy

Rising CPK levels (even in absence of muscle damage), myopathy and rhabdomyolysis has been reported in patients receiving raltegravir (integrase strand inhibitor) [19-22].

The SCOLTA [22] project a prospective, observational, multicentre study assessed the incidence of adverse events in patients receiving new antiretroviral drugs (raltegravir, atazanavir). Symptomatic muscle toxicity was identified in 26 (5.2%) patients. 16 patients had muscle pain and 17 had muscle weakness (7 had both muscle pain and weakness). 72 patients (21.1%) developed increase CPK during follow-up. Seven patients (1.4%) discontinued raltegravir because of muscle pain/weakness and CPK increase. No cases of rhabdomyolysis were observed. In patients on atazanavir, muscle symptoms were more frequently receiving in their regimen with atazanavir than those not receiving it (P=0.04).

Rhabdomyolysis associated with HAART

Protease inhibitors (saquinavir, ritonavir, indinavir, nelfinavir, and amprenavir), didanosine, and lamivudine, are the major drugs implicated [23].

Immune – restoration syndrome (IRIS) following initiation of HAART

IRIS can present with malaise, myalgia and frank myopathy, which typically occurs in early stages of immune reconstitution, during the rapid increase in numbers of CD4⁺ T-cells. Unexpected exacerbation of inflammatory disease and atypical clinical features that resemble the symptoms of autoimmune disease might arise during IRIS. It is more likely to occur in patients with CD4⁺ T-cell count is below 200 following initiation of HAART.

Chronic progressive external ophthalmoplegia (CPEO) associated with HAART

Recently CPEO has been reported in HIV – infected patients with CPEO after long – term use of HAART therapy [24-26].

NRTI – associated cardiomyopathy

Although skeletal muscles has been most commonly studied, given the similarities of mitochondrion in cardiac and skeletal muscle fibres, it seems likely that similar changes can occur in cardiac muscle tissue (probably of milder nature). Limited case reports, show that patients receiving ZDV were also at risk of cardiomyopathy [27].

In contrast, however, there are significant studies in rodents suggesting that NRTIs can affect cardiac muscles.

In a more recent study by Balcarek et al [28], mice fed with ZDV or didanosine for a 9 – week period were found to have enlarged mitochondria (with large scale mitochondrial DNA deletion mutation) and developed cardiomyopathy.

Clinical Features XCAz

Fatigue, Myalgia, tendon pain, nocturnal cramping (symptoms of myopathy tend to be worse at night and are aggravated by exercise) and proximal weakness, often with prominent muscle atrophy are the usual presenting feature of HAART associated myopathy.

ZDV myopathy occurs in about one fifth of patients, when treated with doses of 1200 mg/day for ≥ 6 months.

HAART associated myopathy should be suspected in following settings: [15, 16]

- Lack of pre-existing muscular symptoms
- Presence of a reasonable temporal relationship between the start of treatment or change of dose and the appearance of symptoms
- Lack of any other cause for the myopathy
- Partial or complete resolution of symptoms after the drug is withdrawn.

Risk factors for mitochondrial toxicity include female sex [29], pregnancy [30] and increased age [29].

CPEO presents with symptom of bilateral progressive symmetric ptosis (blepharoptosis) and symptoms related to diplopia or difficulty with pursuit, eccentric gaze, or strabismus (due to external ophthalmoplegia). There is complete lack of fatigue ability, diurnal variation and other features consistent with myasthenia.

Sensorimotor examination usually shows limitation of extra – ocular muscle movement, ranging from mild limitation of horizontal movements to moderate-to-severe limitation in multiple directions and slow saccades horizontally and vertically, with normal smooth pursuit movement.

Rhabdomyolysis usually appears as an acute event; but may have an insidious onset over weeks. Myalgia, muscle weakness, muscle swelling, myoglobinuria (cola colored urine with raised serum and urine myoglobin levels) and a marked elevation in serum CK (between 10 and 100 × ULN) are the usually seen. Secondary renal failure may follow myoglobinuria. Rhabdomyolysis may lead to hyperkalaemia, hypocalcaemia, disseminated intravascular coagulation, cardiomyopathy, respiratory failure and severe metabolic acidosis [31].

Rhabdomyolysis leading to acute renal failure has been reported with the use of protease inhibitors, especially when used in combination with statins.

Shelburne suggested four diagnostic criteria for IRIS [32]:

- pre-existing diagnosis of AIDS
- response to anti-HIV therapy with increased CD4+ counts and decreased HIV-1 viral load
- infectious or inflammatory symptoms that appear during anti-HIV therapy and cannot be explained by another etiology

Diagnosis

Majority has elevated serum creatinine phosphokinase [CK] levels and may occasionally have elevated lactate levels [33, 34].

EMG may be normal or may demonstrate mild myopathic changes. Occasionally a patient may have electromyographic evidence of proximal muscle myopathy despite normal muscle enzymes [35].

High-resolution orbital MRI in CPEO shows an abnormal “spongiform” bright signal on T1-weighted imaging, with preserved extraocular muscle volume, in the absence of orbital inflammation [25].

Muscle biopsy is the gold standard for diagnosis of NRTI – associated

myopathy. Unlike patients with HIV myopathy, light microscopy of the affected muscle in patients with ZDV myopathy generally shows no inflammatory infiltrate or a very mild endomysial collection of T lymphocytes, scattered muscle fiber necrosis, and variable muscle fiber atrophy.

Electron microscopy shows markedly swollen mitochondria with loss of cristae, matrix dissolution, and scattered vesicular inclusions, consistent with the theory that the mitochondrion is the main target of injury.

Histochemistry shows, destructive mitochondrial myopathy with “ragged-red” fibers seen on trichrome stain, indicative of abnormal mitochondria with paracrystalline inclusions [11], and significant lipid and glycogen accumulation in proximity to abnormal mitochondria, as seen in patients with inherited mitochondrial myopathies [36].

Treatment

If NRTI myopathy is suspected clinically or evidence of a mitochondrial myopathy is found on muscle biopsy, the drug should be discontinued and alternate drug initiated. Following discontinuation of NRTIs, CK normalized in about 4 weeks [12] and clinical complaints resolves in about 3 months [37, 38]. In case of partial or no response following drug discontinuation, the probability of HIV myopathy should be considered.

Discontinuation of raltegravir and protease inhibitors results in improvement of the clinical condition with regression of signs and symptoms of skeletal muscle abnormalities.

Systemic corticosteroid therapy is considered in case of persistent myositis [39].

Carnitine, which is required for transport of long-chain fatty acids into mitochondria, is depleted in ZDV associated myopathy [27]. Thus, administration of carnitine has been observed to prevent the development of ZDV myopathy, and prevent progression with continued ZDV administration [33, 40].

Coenzyme Q10, a mitochondrial anti-oxidant has been reported of being used successfully to treat ZDV-associated myopathy without ZDV cessation [41].

If a diagnosis of IRIS is made, HAART is continued and resolution of symptoms requires little or no therapy. However, if there is uncontrolled inflammation in vital areas like central nervous system or eye, HAART should be stopped and use of corticosteroids should be considered.

The management of rhabdomyolysis requires discontinuation of the causative agent, and supportive therapy including intravenous fluids, correction of electrolyte abnormalities and alkalinisation of the urine [31].

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