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NRTI-INDUCED MITOCHONDRIAL TOXICITY AS AN AETIOLOGY FOR FAT REDISTRIBUTION SYNDROME

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BACKGROUND: Morphological appearance of fat redistribution syndrome (FRS) is similar to the non-HIV-related diseases multiple symmetric lipomatosis (MSL) and C3 (complement) deficiency. Persons afflicted with MSL have regional adiposity, peripheral neuropathy, and myoclonic epilepsy with ragged red fibre syndrome. Mitochondrial dysfunction, possibly related to decreased cytochrome c oxidase activity, has been established as the cause. C3-deficient persons are characterized by peripheral lipoatrophy, hyperlipidaemia and insulin resistance.

OBJECTIVES: To explore pharmacological mechanisms of action for FRS.

RESULTS: Long-term use of NRTIs is associated with defects in the mitochondria resembling MSL. Mitochondrial toxicity is both tissue-specific (polymerase γ hypothesis) and insidious in nature (mitochondrial threshold theory). Zidovudine-induced myopathy with ragged red fibres and NRTI-induced peripheral neuropathy are recognized consequences of mitochondrial toxicity. We hypothesize that the development of dorsal lipoma and central adiposity with peripheral lipoatrophy is a consequence of adipocyte dysfunction secondary to NRTI-induced mitochondrial toxicity. Fat with large mitochondrial mass (brown fat and central fat) may have less energy available for lipolysis resulting in lipid accumulation; fat with lesser mitochondrial mass (peripheral fat) may undergo apoptosis resulting in a lipoatrophic appearance and hypertriglyceridaemia. Hyperlipidaemia and insulin resistance can be secondary to reduced uptake of fats and glucose in the affected adipocytes. Alternatively, impaired adipocytes may have reduced synthesis of C3.

CONCLUSION: We hypothesize that NRTIs may precipitate FRS. This hypothesis does not exclude other factors such as HIV protease inhibitors or other factors that may exacerbate this condition. Future studies are needed to elucidate the cause(s) of FRS.

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