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Poster presentation

Quantitative and qualitative mtDNA-lesions with mitochondrial dysfunction in multiple organs after HAART-associated fatal lactacidosis

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Background

We describe a 62 year-old HIV-infected male, being treated with didanosine (ddI), stavudine (d4T) and efavirenz, who died with lactacidosis. Co-morbidities were ethanol-induced liver cirrhosis (Child B) and unclear renal insufficiency (GFR 20 ml/min). After 16 months of therapy he developed hyperlactatemia (3.7 mmol/l [normal <2.2]) without acidosis. Two months later after increasing lactic acidosis (pH 6.9, lactate 27 mmol/l) requiring ICU-treatment, including i.v. uridine (20 g/d), he died in multi-organ failure without signs of infection.

Post-mortem, mtDNA copy numbers of the patient's liver, skeletal muscle (SM), heart (HM) and kidney were measured by PCR and compared with nine control autopsies [1]. MtDNA levels were profoundly depleted: liver 7%, kidney 20%, SM 28%, HM 72%. MtDNA of HM and SM were analysed for large scale deletions (8 HM/3 SM) [1]. Sequencing confirmed the DNA fragments to be mitochondrial. Western Blotting of SM and HM proteins showed depressed mtDNA-encoded respiratory chain component COXII in relation to nucleus (nDNA) encoded COXIV. Spectrophotometry revealed reduced activities of COX and NADH dehydrogenase which require an intact mitochondrial genome in both tissues. nDNA encoded activities were preserved. The ultrastructure of both organs showed mitochondrial swelling and small fat vacuoles. The crystal architecture was lost; some organelles were filled with electron dense material.

Discussion

This is the first investigation of multiple organs in fatal lactic acidosis showing severe biochemical and ultrastructural damage of the mitochondria secondary to HAART-induced quantitative and qualitative mtDNA lesions. Lactic acidosis is a life-threatening complication of HAART with abrupt onset and uncharacteristic symptoms. ddI and d4T are strong inhibitors of polymerase-gamma which induces mtDNA depletion in adipose tissue and liver [1]. Respiratory chain dysfunction promotes liberation of reactive oxygen species at the respiratory chain, which can attack the respiratory chain itself or induce mitochondrial mutations, leading to mtDNA deletions. A vicious circle of interconnected mtDNA and respiratory chain insults may arise and contribute to organ failure. MtDNA depletion is not confined to liver and adipose tissue, but is a multisystem complication. Supportive therapy of hyperlactatemia and lactate acidosis may include uridine supplementation which has demonstrated efficacy on mitochondrial toxicity and hyperlactatemia [2]. (Figure 1.)

	Heart		Skeletal muscle	
	Controls	Patient	Controls	Patient
mtDNA copies/ nucleus	622±77	451	239±73	66
Large scale mtDNA deletions	None	+++	None	++
COXII/COXIV-ratio (% of control mean)	100±6	67	100±19	72
COX activity (μmoles min^{-1} g $protein^{-1}$)	2.7±0.7	0.8	3.1±1.2	1.1
COX/SDH-ratio (% of control mean)	100±33	18	100±76	24
Citrate synthase activity (μmoles min^{-1} g $protein^{-1}$)	147±26	161	152±19	140
NADH dehydrogenase activity (μmoles min^{-1} g $protein^{-1}$)	84±12	90	86±21	106
NADH dehydrogenase /SDH-ratio (% of control mean)	100±39	61	100±56	90

Figure 1
Mitochondrial parameters in patient tissues in comparison with autopsy material from nine controls deemed free of organ pathology. Control values represent group means (± SD).

References

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