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Background

Nucleoside-analogue reverse-transcriptase inhibitors (NRTIs) reduce mother-to-child-transmission (MTCT) of HIV by about 70%. NRTIs are also substrates for DNA polymerase, the enzyme required for replication of mitochondrial DNA (mtDNA). Decreased concentrations of mtDNA were observed in cultured cells exposed to NRTIs, and in muscle cells from patients with zidovudine (ZDV)-induced myopathy. Children with possible mitochondrial dysfunction were described (Blanche al. The Lancet 1999)

Objectives

1. To describe and compare the level and occurrence of elevated lactate (LA) levels between children from HIV positive and negative mothers.
2. To assess the association between prenatal exposure to NRTIs and the occurrence of elevated lactic acid levels.

Methods

Design and setting

Cross-sectional and prospective cohort study

Study cohorts

HIV children:

All children (HIV positive and negative) born with HIV infected women who were followed from birth by the Department of Paediatrics, University of Padova, until 2004

Controls:

Children from HIV negative mothers

Data collection

All children from HIV positive mothers were followed from birth with repeated measurements of LA during routine visits. Medications administered prenatally and during labour were recorded. LA, pyruvate (if necessary) and normal blood chemistry was done on all blood samples. Blood samples from children of all HIV negative mothers were obtained as close to birth as possible and LA levels

were measured. Parental informed consent was obtained for all children.

Analysis

The prevalence of elevated LA levels (>2.5 mmol/l) was calculated at birth (within 90 days) for HIV children and controls. The association of an elevated LA level within 90 days after birth with prenatal and perinatal HAART treatment was estimated through logistic regression analysis among children of HIV positive mothers. These children were divided in HIV positive and negative.

Results

Cohort

Data were collected from a total of 99 children of HIV positive mothers, who were followed from birth. Among the children followed from birth, 4 children were HIV positive, none of these children had received ART prophylaxis during labour and none of the women were treated during pregnancy.

Table 1: Association between ART treatment during pregnancy and abnormal LA levels within 90 days after birth

Cohort	N	Mean lactate level	SD lactate level	No. with lactate > 2.5 mmol/l	% with lactate > 2.5 mmol/l
Control	24	1.65	0.41	0	0
Children from HIV pos. mothers not infected	84	3.13	1.58	47	56.0
Treated in pregnancy	59	3.21	1.71	34	57.6
Not-treated (excl bolus AZT)	25	2.95	1.16	13	52.0

84 HIV negative children had measurements of lactate levels within 3 months after birth and these children define the final HIV children cohort. Maximum LA levels were 8.50

mmol/l and all levels normalized during follow-up. None of the children with elevated LA levels developed clinical evidence of mitochondrial damage.

The control cohort comprised of 24 children who had lactate assessments within 3 months after birth, LA levels were significantly lower than in children of HIV positive mothers.

No class of antiretroviral therapy was significantly associated with elevated LA (table 1)

Table 1: Association between therapy during pregnancy and LA elevation among children born with HIV positive mothers.

ARV Tx	Controls (n=39)	Cases (n=47)	OR	95%CI
PI	17.9	17.0	0.94	0.31-2.87
NNRTI	23.1	25.5	1.14	0.42-3.08
NRTI	64.1	72.3	1.47	0.59-3.66
D4T	20.5	19.1	0.92	0.32-2.66
3TC	59.0	61.7	1.12	0.47-2.67
Ddl	2.6	2.1	0.83	0.05-13.7
DdC	2.6	0	-	
AZT	46.2	55.3	1.44	0.62-3.39

* reference: persons not taking the specific compound

Conclusions

- 1) Children from HIV positive mothers have significantly higher LA levels within 90 days after birth than children from HIV negative mothers.
- 2) LA levels are also elevated in children from HIV positive mothers who were not treated during pregnancy. This may be due to ART administration during labour or in the first 6 weeks of life.
- 3) Maternal ARV treatment did not significantly increase the risk of LA elevation among newborns. Prevention of vertical transmission should continue.

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