Abnormal fatty acid oxidation in HIV-exposed, uninfected neonates in the US

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ABSTRACT*

Background: Abnormal newborn screens for dysfunctional fatty acid oxidation (FAO) are more common in HIV-exposed uninfected (HEU) neonates than the general population and may be related to *in utero* exposure to HIV and/or combination antiretroviral therapy (cART). Normal FAO is necessary for normal growth and development. Disordered FAO can result in hypoglycemia, myopathy and liver injury.

Methods: We analyzed serum acylcarnitine profiles (ACP), as a measure of FAO, in 522 HEU neonates (age 0-7 days) enrolled in the Surveillance Monitoring for Antiretroviral Therapy Toxicities (SMARTT) study of the Pediatric HIV/AIDS Cohort Study (PHACS). We estimated the prevalence of abnormal ACP and evaluated associations of abnormal ACP with *in utero* exposure to cART and antiretroviral (ARV) drug classes in logistic regression models, adjusting for maternal demographic characteristics, disease status and substance use. We also evaluated associations of abnormal ACP with clinical laboratory parameters (lactate, glucose, creatine kinase (CK) and alanine aminotransferase (ALT)) and measures of neurodevelopment and growth through 3 years of age.

Results: 89 (17%) had abnormal ACP, with most abnormal profiles characterized by generalized or long-chain specific acylcarnitine elevations. Maternal alcohol exposure (adjusted odds ratio (aOR)=2.55, 95% confidence interval (CI): 1.21, 5.37, p=0.01) and, as expected, lower gestational age at birth (aOR=1.21 per week lower, 95% CI: 1.07, 1.36, p<0.01) were associated with higher odds of having an abnormal ACP. In analyses adjusted for alcohol exposure and gestational age, in utero exposure to a protease inhibitor (PI) was associated with higher odds of having an abnormal ACP (aOR= 2.35, 95% CI: 0.96, 5.76, p=0.06) while exposure to a non-nucleoside reverse transcriptase inhibitor (NNRTI) (aOR=0.23, 95% CI: 0.07, 0.80, p=0.02) was associated with lower odds. ALT levels were higher in those with abnormal vs. normal ACP (geometric mean 18.7 U/L vs. 14.9 U/L, p<0.01,), but no differences in lactate, glucose or CK were observed. ACP status was not associated with MacArthur-Bates Index and Bayley Score at 1 year or anthropometric measurements at 2 and 3 years of age.

Conclusions: Abnormal ACP, indicating dysfunctional FAO, are relatively common in HEU neonates and are associated with PI use and maternal alcohol exposure during pregnancy as well as higher neonatal ALT levels, suggesting the possibility of subclinical hepatic dysfunction. Abnormal ACP is not associated with levels of CK, glucose, lactate or significant delays in growth or development. Further studies are needed to determine the long-term clinical implications of abnormal FAO in HEU neonates.

* Data presented in abstract based on data available by January 1, 2013.

BACKGROUND

- Nucleoside reverse transcriptase inhibitors (NRTIs) inhibit polymerase gamma and cause mitochondrial toxicity (1)
- PIs are associated with metabolic toxicity: hyperlipidemia, insulin resistance and abnormal lipolysis in both adults and children (1)
- FAO is an intra-mitochondrial pathway situated at the crux of lipid catabolism, glucose utilization and mitochondrial OXPHOS and catabolizes fatty acids to acetyl-CoA during starvation and increased metabolic demand. FAO plays an important role in fetal-placental health (2)
- State newborn screening (NBS) programs use ACP to identify neonates with inherited disorders of FAO
- An increased incidence of abnormal newborn screens for FAO in HIV-exposed neonates has been reported (3)

OBJECTIVES

- To determine the prevalence and patterns of abnormal ACP in HEU neonates
- To determine if abnormal ACP (indicative of dysfunctional FAO) is associated with certain ARV regimens or adverse clinical outcomes

METHODS

Study Population

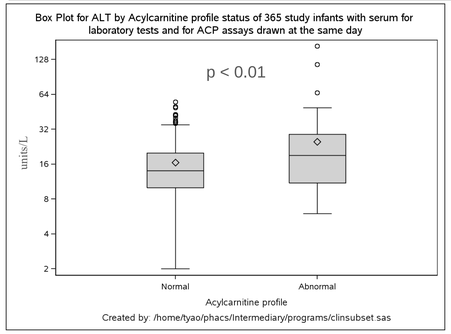
- 522 HEU neonates born to HIV-infected pregnant women enrolled into the Dynamic Cohort of SMARTT
- Infants who had accessible serum specimens within 7 days from birth as of July 1st, 2011

Definitions and Statistical Methods

- ACP on serum samples evaluated using tandem mass spectrometry (MS/MS) as previously described (3)
- Abnormal ACP defined as a profile with clinically significant analyte(s) >95th percentile for age-matched reference range
- Associations of abnormal ACP with *in utero* exposure to cART and ARV drug classes were evaluated in logistic regression models, adjusting for maternal demographic characteristics, disease status and substance use during pregnancy
- Associations of abnormal ACP with clinical laboratory parameters, neurodevelopment and growth through 3 years of age were evaluated using generalized linear models, adjusting for covariates including ARV exposure

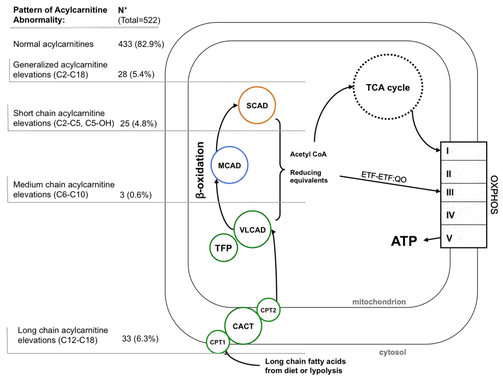
RESULTS

Figure 1: ALT Levels in HEU Neonates by ACP Status



RESULTS

Figure 2: Patterns and proportions of abnormal ACP in 522 HEU newborns in the PHACS SMARTT Dynamic Cohort



- The pattern of acylcarnitine elevations can point to the level of biochemical dysfunction in FAO
- Generalized acylcarnitine elevations can be seen in ETF-ETF:QO dysfunction or in primary dysfunction of oxidative phosphorylation
- Short-chain acylcarnitine elevations can indicate dysfunction in SCAD (C4) or in pathways of organic acid catabolism (C3, C5, C5-OH [not pictured])
- Medium-chain acylcarnitine (C6-C10) elevations indicate dysfunction in MCAD.
- Long-chain acylcarnitine elevations (C12-C18, where the number corresponds to the number of carbons chain length of fatty acid) indicate dysfunction in the carnitine shuttle (CPT1, CACT, CPT2), which transports long-chain fatty acids into the mitochondria, or the first steps (TFP, VLCAD) of beta-oxidation which convert long-chain fatty acids into medium chain fatty-acids

Abbreviations: *ATP, adenosine triphosphate; OXPHOS, oxidative phosphorylation; TCA, tricarboxylic acid cycle; CPT, carntitine palmitoyltransferase; CACT, carnitine-acylcarnitine translocase; TFP, trifunctional protein; VLCAD, very long-chain acyl-CoA dehydrogenase; MCAD, medium-chain acyl-CoA dehydrogenase deficiency; SCAD, short-chain acyl-CoA dehydrogenase deficiency; ETF, electron transport flavoprotein; ETF:QO, electron transport flavoprotein oxidoreductase*

Table 1. Adjusted Associations for Abnormal ACP by Maternal and Demographic Risk Factors in 498 SMARTT Infants

	Adjusted Odds Ratio	95% Confidence Interval	P-value
Demographic Characteristics			
Gestational age (per week lower)	1.21	(1.07,1.36)	0.002
Maternal age at delivery (years)			0.080
< 21 yr vs 21-37 yr	0.71	(0.30, 1.70)	0.717
> 37 yr vs 21-37 yr	0.36	(0.14, 0.91)	0.090
Maternal Exposures and Risk Behaviors During Pregnancy			
Alcohol use	2.55	(1.21, 5.37)	0.014
Smoking (active or passive)	1.65	(0.98, 2.77)	0.058
Maternal Health Status During Pregnancy			
Earliest available CD4% < 25%	1.64	(0.98, 2.75)	0.058
Earliest available RNA >= 1000 cp/mL	0.61	(0.36, 1.01)	0.056

Table 2. Associations between Abnormal ACP and ARV Regimens Adjusted for Other Risk Factors in 494 SMARTT Infants

Variable	Odds Ratio	95% Confidence Interval	P-value
Combination ARV regimen		-	0.024
HAART with NNRTI (w/ & w/o PI)	0.22	(0.06,0.75)	0.015
Other Regimen	0.49	(0.18,1.32)	0.159
HAART with PI (No NNRTI)	1.00	(ref)	
Individual class or drug			
NNRTI use	0.23	(0.07,0.80)	0.020
PI use	2.35	(0.96,5.76)	0.062
ZDV use	0.88	(0.51,1.53)	0.662
Duration of ZDV use (week)	0.98	(0.96,1.00)	0.122
3TC	0.67	(0.39,1.15)	0.146
Duration of 3TC use (week)	0.97	(0.95,0.99)	0.011

**Adjusted models are multiple logistic models on one single ARV variable adjusted for gestational age, maternal age, alcohol use, smoking exposure, earliest CD4% and earliest viral load during pregnancy.*

SUMMARY

- 17% of HEU newborns have abnormal ACP indicating dysfunction in fatty acid oxidation. ~0.5% of newborns are expected to have an abnormal ACP on their NBS (3)
- Abnormal ACP in HEU neonates are associated with gestational age, maternal exposure to smoking and alcohol
- CD4%<25% and VL>1000 copies/mL are associated with higher and lower odds of having an abnormal ACP, respectively
- Abnormal ACP in HEU neonates are associated with exposure to PI-containing ARV regimens
- Abnormal ACP in HEU neonates are associated with increased ALT levels but *not* increased lactate, CK or glucose levels (data not shown)
- Abnormal ACP in HEU neonates are *not* associated with abnormal growth or neurodevelopment during early childhood

CONCLUSIONS

- These findings reveal dysfunctional FAO in HEU especially in those exposed to PIs and suggest the possibility of subclinical hepatic dysfunction in HEU newborns
- Abnormal FAO is seen in mitochondrial dysfunction and insulin resistance-- both associated with PI exposure
- Abnormal ACP in HEU is not associated with common clinical complications of abnormal FAO (hypoglycemia, elevated CK) mitochondrial dysfunction (hyperlactatemia) or neurodevelopment outcomes up to 3 years of age
- Further studies are needed to determine the long-term clinical implications of abnormal FAO in HEU neonates given that abnormal intrauterine metabolism/nutrition may have implications for the health of these infants in adulthood (4,5)

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