

HYPOPLASTIC LEFT HEART SYNDROME AND COARCTATION OF THE AORTA: TOXICOGENOMIC STUDIES SUGGEST AN ENVIRONMENTAL FACTOR

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Background : We sought to identify possible gene-environment interactions for congenital heart malformations (hypoplastic left heart (HLH) and coarctation of the aorta (CoAo)). We have previously shown geospatial aggregations of HLH and CoAo, higher maternal solvent exposure, and potential interaction with GST-theta activity. (Loffredo)

Methods: Mother/infant pairs, where infants were < 1yr of age were studied. Cases were infants undergoing cardiac surgery for HLH or CoAo (N=14 pairs). Controls were unrelated cardiac malformation (N=16 pairs). Bloods were obtained at the time of surgery. Mothers completed a questionnaire about environmental exposures. Blood DNA was genotyped for 14 toxicogenomics loci. Blood concentrations of 37 lipid-adjusted PCB isomers, and 9 pesticides were determined in all pairs. Statistical analyses were made for the sum of total PCBs, dioxin like (DLPCB) and non dioxin like (NDL) PCBs. Blood AhR transactivation was also measured.

Results: Mean infant age was 53 days for cases and 92 days for controls. Total PCBs, DLPCBs, NDLPB levels were associated with CoAo (*N=7) (P= 0.008 for total PCB), but not with HLH (N=7). Covariates for PCB levels included history of alcohol consumption and maternal age. By non parametric analysis, blood concentrations of summed pesticides were associated with case status (p=0.0034), and separately for HLH and for CoAo specifically (ppDDE and t-NONA). 4 gene loci showed positive associations of low metabolizer alleles with infant cases (ARNT T19, PON1 rs# 662, CAT C26T rs # 1001179 and CYP1A2 rs # 726551).

Conclusions: Our data are consistent with gene-environment interactions leading to geospatial clustering of congenital heart malformations. Blood levels of PCBs and pesticides in infants with HLH or CoAo and their mothers were higher than controls. DL and NDL PCB and pesticides were associated with CoAo; DDE and t NONA were associated with both HLH and CoAo. This pilot study should be confirmed in larger cohorts

