GENETIC MARKERS RELATED TO MORPHINE BIOTRANSFORMATION INTERACTED WITH NEONATAL CLINICAL FACTORS TO PREDICT BEHAVIORAL PROBLEMS IN VERY PRETERM CHILDREN AT 18 MONTHS

Cecil MY Chau, MSc
University of British Columbia
Student/Trainee

INTRODUCTION / AIM

Background: Behavior problems are prevalent among children born very preterm (≤ 32 weeks gestation [GA]), and are associated with neonatal procedural pain and morphine exposure. Morphine accumulation in the brain is determined by genetic variation related to morphine biotransformation.

Aim: To investigate whether morphine-biotransformation genotypes contribute to individual differences in long-term effects of morphine on behavior at 18 months.

METHODS

198 children born very preterm (24-32 weeks gestation [GA]) followed from birth and seen at 18 mo corrected age. Relationships between Child Behavior Checklist (CBCL; Internalizing, Externalizing) and neonatal invasive procedures, morphine exposure, sex, GA, illness severity, postnatal infection, surgeries, and morphine biotransformation gene variants (genotyped from saliva) in ABCB1 (rs2032582, rs1045642, rs1128503), OPRM1 (rs563649, rs1799971), UGT1A9 (rs17863783), ABCC2 (rs2273697, rs17222723, rs8187710), ABCC3 (rs2277624, rs11568591), SLCO1B1 (rs4149056), CYP3A4 (rs2242480), COMT (rs4680) were examined using constrained principal component analysis.

RESULTS

Neonatal clinical predictors and genotypes accounted for 35% of the overall variance in behavior. Neonatal invasive procedures (p=1.4 x 10-6) and infection (p=.003) were associated with more Internalizing behavior. ABCB1 rs1128503 C allele (↑ morphine accumulation in the brain; p=.002) and OPRM1 rs563649 T allele (↓ Mu Opioid Receptor production thus ↑ pain sensitivity; p=3.0 x 10-6) were associated with less Internalizing behavior. In children with UGT1A9 rs17863783 (a marker of UGT1A6*4, UDP-glucuronosyltransferase), more morphine exposure (p=.0003) and higher number of surgeries (p=.0001) were associated with more Internalizing behavior. More externalizing behavior was predicted by higher invasive procedures in children with the COMT rs4680 Met/Met genotype (p=.0006), and by ABCB1 rs1045642 minor allele (↑ morphine accumulation in the brain; p=.0005) together with neonatal infection.

DISCUSSION / CONCLUSIONS
Genetic variations that affect relative accumulation of morphine in the brain, together with neonatal clinical factors, are differentially related to internalizing and externalizing behaviors at 18 months in children born very preterm.

OTHER AUTHORS

Colin JD Ross
Steven P Miller
Vann Chau
Anne R Synnes
Bruce Carleton
Ruth E Grunau