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Neonatal abstinence syndrome (NAS) in methadone exposed infants: role of genetic variability



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Opioid dependence in pregnancy

- **Methadone (MD):**
 - Currently the only FDA/TGA “approved” opioid substitution therapy during pregnancy.
 - Advantages: ↓ obstetric complications, ↑ prenatal care, ↑ maternal nutrition, ↓ drug seeking environment.
 - Disadvantages: Neonatal Abstinence Syndrome (NAS).

Understanding opioid dependence

- ↓ understanding of opioid dependence in adults.
- ↑ inter-individual variability in response to MD:
 - Impact of genetic variability.
- Drug targets/receptors (*OPRM1*) ?
- Drug transporters (*ABCB1*) ✓
- Metabolising enzymes (*CYP2D6*) ?
- Immune response (*IL-1B*) ✓
 - Glial activation → release of immune mediators incl. proinflammatory cytokines interleukin-1 beta (*IL-1β*), creates proinflammatory environment → neuronal excitability to ↑ opioid reward and dependence.

Genetic variability and NAS

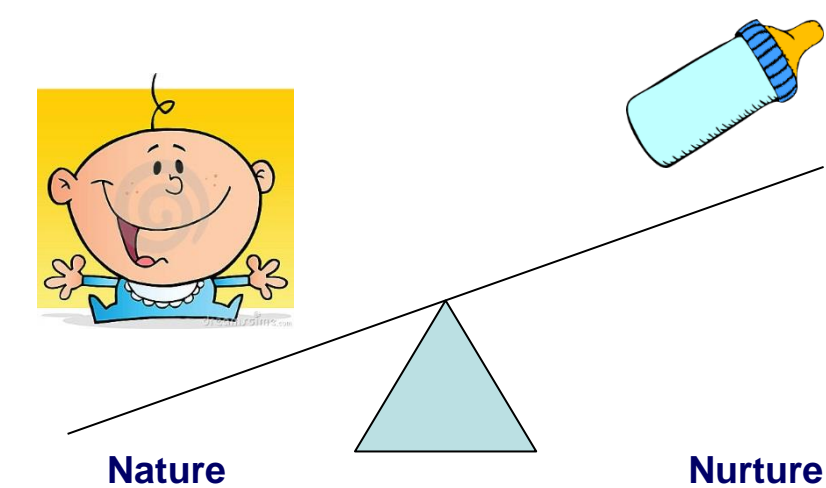
- Despite ↑ knowledge on the impact of genetic variability on MD response, the underlying mechanisms explaining NAS largely undefined:
 - ? genetic variability.
- By assessing genetic variability in mothers and infants, the association between genetic variability and NAS could be used as a predictive tool:
 - = ↑ management of the infant by potentially ↓ morphine administered to control NAS.

Aim

- Investigate the impact of *IL-1B*-31 and *OPRM1* A118G genetic variability on NAS incidence (treatment required) & severity (dose of morphine).

Nature vs Nurture

Dependence = genetics + environment
!!!! Uniqueness of current study



Genotyping for *OPRM1* and *IL-1B*

- Infant buccal swab: DNA isolated from cheek cells, genotyped
- Genetic markers:
 - *OPRM1* A118G: Wild-type (WT) associated with ↑ response to opioids
 - Immune response, *IL-1B*-31 promoter mutation: Wild-type (WT) associated with ↑ *IL-1β* expression

Infant characteristics

Maternal methadone dose at delivery: mg (median (range))	120 (20-220)
Gestational age: weeks (median (range))	39 (35-41)
• Premature (n (%))	2 (8)
Gender male (n (%))	14 (54)
Birth weight: g (median (range))	2963 (2157-3883)
• Low birth weight (n (%))	5 (19)
Exposure to (n (%)):	
• Benzodiazepines	11 (42)
• Nicotine	15 (83)
Adjunctive phenobarb (n (%))	6 (23)

- 71 methadone exposed infants; 46 with NAS; 26 with genetic & morphine treatment data.
- No difference in *IL-1B* or *OPRM1* genotypes between infants with & without NAS, OR (p):
IL-1B: 1.9 (0.21)
OPRM1: 0.23 (0.24)

Morphine Treatment

<i>IL-1B</i> -31 Infant genotype (morphine (mg), median (range))					
WT (n=21)	> 1 Var (n=5)	WT (n=21)	> 1 Var (n=5)	WT (n=20)	> 1 Var (n=5)
0.15 (0.1-0.4)	0.2 (0.14-0.3)	0.3 (0.17-0.66)	0.28 (0.23-0.68)	33.8 (14.3-79.3)	34.8 (26.7-91.8)
Initial morphine (p=0.06)		Max morphine (p=0.94)		Total morphine (p=0.67)	

<i>OPRM1</i> A118G Infant genotype (morphine (mg), median (range))					
WT (n=24)	> 1 Var (n=2)	WT (n=24)	> 1 Var (n=2)	WT (n=23)	> 1 Var (n=2)
0.17 (0.1-0.4)	0.22 (0.13-0.3)	0.29 (0.17-0.68)	0.24 (0.18-0.3)	34.8 (14.3-91.8)	25.4 (19.4-31.5)
Initial morphine (p=0.73)		Max morphine (p=0.39)		Total morphine (p=0.38)	

Conclusion

- Despite impact of *IL-1B* and *OPRM1* genetic variability on opioid response in adults, this was not observed in infants.
- Limitation: small sample size to date.
- This study of possible impact of *IL-1B* and *OPRM1* genetic variability on NAS is ongoing, and could lead to tools to predict NAS incidence & severity.

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