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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-1β)?
  - 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-1β -31 and OPRM1 A118G genetic variability on NAS incidence (treatment required) & severity (dose of morphine).

Nature vs Nurture

Dependence = genetics + environment

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-1β -31 promoter mutation: Wild-type (WT) associated with ↑ IL-1β expression

Infant characteristics
- Maternal methadone dose at delivery: mg (median (range))
  - WT (n=20): 120 (20-220)
  - WT (n=20): 39 (35-41)
  - WT (n=20): 2 (8)
- Gestational age: weeks (median (range))
  - Premature (n (%))
    - WT (n=21): 14 (54)
    - WT (n=21): 11 (42)
    - WT (n=21): 15 (53)
    - WT (n=21): 6 (23)
- Gender male (n (%))
- Birth weight: g (median (range))
  - Low birth weight (n (%))
  - WT (n=20): 2963 (2157-3883)
  - WT (n=20): 14 (54)
  - WT (n=20): 11 (42)
  - WT (n=20): 15 (53)
  - WT (n=20): 6 (23)

IL-1β -31 Infant genotype (morphine (mg), median (range))

<table>
<thead>
<tr>
<th></th>
<th>WT (n=21)</th>
<th>WT (n=21)</th>
<th>WT (n=20)</th>
<th>WT (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15 (0.1-0.4)</td>
<td>0.2 (0.14-0.3)</td>
<td>0.3 (0.17-0.66)</td>
<td>0.28 (0.23-0.68)</td>
<td>33.8 (14.3-79.3)</td>
</tr>
<tr>
<td>Initial morphine (p=0.06)</td>
<td>Max morphine (p=0.94)</td>
<td>Total morphine (p=0.67)</td>
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</tr>
</tbody>
</table>

OPRM1 A118G Infant genotype (morphine (mg), median (range))

<table>
<thead>
<tr>
<th></th>
<th>WT (n=24)</th>
<th>WT (n=24)</th>
<th>WT (n=23)</th>
<th>WT (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.17 (0.1-0.4)</td>
<td>0.22 (0.13-0.3)</td>
<td>0.29 (0.17-0.68)</td>
<td>0.24 (0.18-0.3)</td>
<td>34.8 (14.3-91.8)</td>
</tr>
<tr>
<td>Initial morphine (p=0.73)</td>
<td>Max morphine (p=0.39)</td>
<td>Total morphine (p=0.38)</td>
<td></td>
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</tr>
</tbody>
</table>

Conclusion
- Despite impact of IL-1β 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-1β and OPRM1 genetic variability on NAS is ongoing, and could lead to tools to predict NAS incidence & severity.

References