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Neonatal abstinence syndrome 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:
  - o = ↑ 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

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))
- Gestational age: weeks (median (range))
- Premature (n (%))
- Gender male (n %)
- Birth weight: g (median (range))
- Low birth weight (n %)
- Exposure to (n %):
  - Benzodiazepines
  - Nicotine
  - Adjunctive phenobarb (n %)

Morphine Treatment

- IL-1B-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)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tbody>
<tr>
<td>WT (n=21)</td>
<td>&gt; 1 Var (n=5)</td>
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<tr>
<td>WT (n=21)</td>
<td>&gt; 1 Var (n=5)</td>
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<tr>
<td>WT (n=20)</td>
<td>&gt; 1 Var (n=5)</td>
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<table>
<thead>
<tr>
<th>Initial morphine (p=0.06)</th>
<th>Max morphine (p=0.94)</th>
<th>Total morphine (p=0.67)</th>
</tr>
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<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>
</tr>
<tr>
<td>0.28 (0.23-0.68)</td>
<td>33.8 (14.3-79.3)</td>
<td>34.8 (26.7-91.8)</td>
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</tbody>
</table>

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<tr>
<th>OPRM1 A118G Infant genotype (morphine (mg), median (range))</th>
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<tbody>
<tr>
<td>WT (n=24) &gt; 1 Var (n=2)</td>
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<tr>
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<tr>
<td>WT (n=23) &gt; 1 Var (n=2)</td>
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<tr>
<th>Initial morphine (p=0.73)</th>
<th>Max morphine (p=0.39)</th>
<th>Total morphine (p=0.38)</th>
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<tbody>
<tr>
<td>0.17 (0.1-0.4)</td>
<td>0.22 (0.13-0.9)</td>
<td>0.29 (0.17-0.68)</td>
</tr>
<tr>
<td>0.24 (0.18-0.3)</td>
<td>34.8 (14.3-91.8)</td>
<td>25.4 (19.4-31.5)</td>
</tr>
</tbody>
</table>

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.

References


Aim

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