Evaluation of the R4S post-analytical tool in suggesting inborn errors of metabolism among Sudden Infant Death Syndrome cases and controls

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Introduction

- Current interpretation of tandem mass spectrometry (MS/MS) newborn screening (NBS) results
  - MS/MS has been used in CA since July, 2005.
  - Screening decision is based on cut-off values.
  - Cut-off values vary from disorder to disorder and are rather subjective.
  - False positive and false negative are common.
Introduction

• The R4S post-analytical tool
  – A multivariate pattern-recognition tool developed by the Region 4 Stork (R4S) MS/MS data project.
  – A collaborative effort of 154 public health programs and private laboratories worldwide.
  – Objective was to minimize false positives and false negatives.
  – Determination is based on the degree of overlap between normal population and disease range.
  – Easy to use.
Enhanced interpretation of newborn screening results without analyte cutoff values

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Introduction

- Sudden infant death syndrome (SIDS)
  - Historically associated with metabolic disorders.
  - Remains the third leading cause of overall infant mortality and accounts for 8.4% of all infant deaths.
  - In pre-NBS era, 1-2% were attributed to inborn errors of metabolism (IEMs) especially fatty acid oxidation disorders using postmortem specimens.
  - In post-NBS era, could undiagnosed IEMs remain a contributor to SIDS?
Introduction

• Study objectives
  - To evaluate whether the R4S post-analytical tool is useful in suggesting IEMs that were not detected by regular NBS test among SIDS cases
  - To determine whether suggested IEMs are more common among SIDS cases compared to controls
Methods

• A matched case-control study

• All SIDS cases born during 2005–2008 with available MS/MS NBS testing results were included.

• Five controls were matched to each case on specimen collection date and laboratory code.

• Exclusion criteria
  – Known chromosomal and neural tube defects
  – Confirmed genetic disorders
  – Twin or multiple births
  – MS/MS analyte patterns implying a total parenteral nutrition (TPN) diet
Methods

• Data sources
  – California death record databases.
  – California NBS databases.
  – Patient Discharge and Emergency Department Visit databases from the Office of Statewide Health Planning and Development.
  – Probability matching was used for linking.
  – Linking variables included baby’s date of birth, first name, last name, mother’s maiden name, and residential address, city and zip code.
Methods

• Definitions

  - **SIDS**: ICD-10 code of R95 listed as underlying cause of death on death certificate.
  - **Potential IEM**: with a guideline score of $\geq 2$.
  - **Potentially fatal IEMs (PFIEMs)**: IEMs that were identified in the SIDS case group and might increase the risk of mortality.
  - **Low birth weight (LBW)**: $< 2500$ grams
  - **Small for gestational age (SGA)**: having a weight for gestational age that was below the 10th percentile based on published smoothed birth weight for gestational age norms.
Methods

• Data analysis
  – Frequencies of PFIEMs were reported for both case and control groups.
  – Birth prevalence of PFIEMs was calculated and Chi-square test was used to compare between cases and controls.
  – Multivariable logistic regression was used to assess the association between PFIEMs and SIDS adjusting for LBW; the association between LBW and NICU admission and PFIEMs adjusting for case status.
Results

- Study sample

**SIDS cases**

- **527** Identified from death certificates
- **419** MS/MS results were analyzed
- **415** Included in final analysis
- **108** Excluded due to lack of linkage or MS/MS results, of twin or multiple births, known genetic disorders

**Controls**

- **2095** Randomly selected from NBS database
- **2036** MS/MS results were analyzed
- **2001** Included in final analysis
- **35** Excluded due to potential TPN diet
- **59** Excluded due to twin/multiple births
Results

- Characteristics of the study sample

![Graph showing characteristics of the study sample with SIDS cases and controls. The graph indicates statistically significant differences between the two groups.](image)

**P < 0.01**
## Results

- **Frequency and prevalence of PFIEMs**

<table>
<thead>
<tr>
<th>Type of PFIEMs</th>
<th>SIDS Cases (n=415)</th>
<th>Controls (n=2001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrullinemia Type II (CIT Type II)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Carnitine palmitoyl transferase deficiency-type 1 (CPT-1 deficiency)</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Hypermethioninemia (MET)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Ornithine transcarbamylase /carbamoyl phosphate synthetase deficiency (OTC/CPS deficiency)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Argininosuccinic acid lyase deficiency (ASA)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Prevalence of all PFIEMs</strong></td>
<td>1.5%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>
## Results

- **Multivariable analysis (SIDS Cases Vs. Controls)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SIDS Cases Vs. Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>Suggested PFIEMs</td>
<td>1.1</td>
</tr>
<tr>
<td>Low birth weight (LBW)</td>
<td>2.8</td>
</tr>
<tr>
<td>Small for gestational age (SGA)</td>
<td>1.3</td>
</tr>
<tr>
<td>NICU admission</td>
<td>2.3</td>
</tr>
<tr>
<td>Had emergency room visits during infancy</td>
<td>2.0</td>
</tr>
<tr>
<td>Had hospital admissions during infancy</td>
<td>1.4</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adjusted for LBW and NICU admission; <sup>b</sup> Adjusted for PFIEM status; 
<sup>c</sup> Adjusted for LBW and PFIEM status
Results

- Comparison between PFIEMs and non-PFIEMs

* P<0.05  ** P<0.01
**Results**

- **Multivariable analysis (PFIEMs Vs. Non-PFIEMs)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PFIEMs Vs. Non-PFIEMs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>3.4</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>2.1</td>
</tr>
<tr>
<td>NICU admission</td>
<td>4.4</td>
</tr>
<tr>
<td>Had emergency room visits during infancy</td>
<td>0.8</td>
</tr>
<tr>
<td>Had hospitalizations during infancy</td>
<td>1.7</td>
</tr>
</tbody>
</table>

**Note:** Adjusted for case status and LBW except for low birth weight variable
Conclusions

- The R4S tool suggested five types of PFIE Ms among SIDS cases that were not previously reported.
- The PFIE Ms were not more prevalent among SIDS cases compared to controls.
- These PFIE Ms might have contributed to the sudden deaths among infants with the presence of other birth compromising conditions.
- The suggested PFIE Ms might reflect serious metabolic dysfunction but did not reach diagnosis level.
Limitations and Next Step

- Nearly 20% of all identified cases were excluded, which might have reduced the statistical power of analysis.
- The sensitivity and specificity of the R4S tool for the suggested PFIEIMs are unknown. It is unclear how many of the suggested PFIEIMs are truly metabolically compromised.
- Further investigation is needed to evaluate the sensitivity and specificity of the R4S tool for the suggested conditions.
Acknowledgement

- Region 4 Stork MS/MS data project
  - Piero Rinaldo, MD
  - David M.S. McHugh
- California Office of Statewide Health Planning & Development
- California Office of Vital Records
References


• Have a safe trip home!
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Thank you!