Perinatal acute respiratory failure, autopsy remains the best quality control

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BACKGROUND

• Autopsy
  • Autopsy rates have been declining significantly in recent decades
    • Adult autopsies:
      • 1959: 50%
      • 1992: 1.5%
    • Pediatric autopsies
      • Less significantly decrease:
      • 25-53% EXCLUDING MEDICAL LEGAL CASES
BACKGROUND:

• Why we did this study?
  • Acute Respiratory Failure is one of the most common problems seen in premature and term babies
    • Etiology: Surfactant deficiency, MAS, sepsis, persistent pulmonary hypertension, pulmonary hypoplasia, others
  • Autopsy examination is an important quality control
  • Often establishes the etiology for the perinatal respiratory depression and cause of death
AIM:

- Correlate autopsy findings with initial clinical impression in cases of failure to resuscitate in early perinatal period
MATERIAL AND METHODS:

• 200 autopsy reports were reviewed from 2000-2019

• Inclusion criteria:
  • Age > 0-10 days
  • Clinical history of respiratory failure unresponsive to treatment

• Exclusion Criteria
  • Cases with imaging only autopsies
RESULTS

Clinical Pathological Correlation

- Agree: 45
- Disagree: 55
MAJOR DISCREPANCIES

- Infection: 4%
- Congenital Heart Disease: 2%
- Congenital lung abnormalities: 1%
• Infection
  • Routine in autopsies: lung and blood cultures
• Most frequent post mortem cultures:
  • E. coli: most frequent 3%
  • Herpes
  • GBS
  • Candida
  • MRSA
  • Pseudomonas

RESULTS

Post mortem cultures

E. coli  Herpes  GBS

0  0,5  1  1,5  2  2,5  3  3,5

Post mortem cultures
RESULTS

- Placenta
  - 50% of the cases had acute placental inflammation
- Clinical cause of Death
  - 4% DIC
  - 3% pneumonia
  - 2% necrotizing enterocolitis
# RESULTS

- **Lethal Complex Malformations**

<table>
<thead>
<tr>
<th>Pre mortem Diagnosis</th>
<th>Postmortem Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td>IUGR and craniocerebellarcardiac syndrome Ritsher-Schinzel</td>
</tr>
<tr>
<td>Congenital Heart Disease</td>
<td>Necrotizing enterocolitis totalis</td>
</tr>
<tr>
<td>Twin B, perinatal hypoxia</td>
<td>Copy number loss with Chromosomal band 8p22 of unclear significance; cause of death: bronchopneumonia and DIC, negative cultures</td>
</tr>
<tr>
<td>Respiratory Insufficiency</td>
<td>Trisomy 13, Double outlet right ventricle, pulmonary valve atresia Hypoxic-ischemic encephalopathy</td>
</tr>
<tr>
<td>Fetal bradycardia</td>
<td>Dextrocardia, L-transposition of great arteries, Ebstein’s anomaly and dysplastic valves, pulmonary hypoplasia</td>
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<td>Respiratory insufficiency, fetus of diabetic mother</td>
<td>Di George Syndrome, absent kidneys, severe pulmonary hypoplasia</td>
</tr>
<tr>
<td>Non-reassuring fetal heart rates</td>
<td>Neonatal sudanophilic orthochromatic leukodystrophy bacterial sepses and pneumonia</td>
</tr>
<tr>
<td>Fetal bradycardia</td>
<td>Complex cardiac congenital disease, pulmonary hypoplasia, marked cardiomegaly</td>
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</table>
RESULTS

• Lethal lung abnormalities

• All of them the clinical picture was "respiratory insufficiency at birth even with intensive support"
  • Acinar Dysplasia
  • Alveolar Capillary Dysplasia
  • Alveolar Capillary Dysplasia with misalignment of pulmonary veins
ACINAR DYSPLASIA

- Diffuse bilateral impairment of the development of respiratory bronchioles, alveolar ducts and alveoli
- Females
- Neonatal lethal due to respiratory insufficiency at birth, generally survive only hours, even with support
ACINAR DYSPLASIA

- The *TBX4* gene (MIM 601719) spans about 50 kb on chromosome 17q23.2 and consists of eight (or possibly nine) exons.

- During organogenesis, *TBX4* is expressed in the hind limbs, mandibular mesenchyme, lung mesenchyme, atrium of the heart and body wall.
ALVEOLAR CAPILLARY DYSPLASIA WITH MISALIGNMENT OF PULMONARY VEINS

Full term, AGA, respiratory distress within a few hours of birth and death within days to weeks

- 80% have malformations outside the lung
  - Heart defects (19% with HLH, PFO, PDA), tracheoesophageal fistula (3%), gut malrotation (22%), absent gall bladder, renal agenesis, hydronephrosis (24%), imperforate anus (8%), and single umbilical artery (19%), cerebellar heterotopia (3%)
  - Lungs may also have abnormal lobation and lymphangiectasis (33%), rarely small
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• Heterozygous point de novo mutations or genomic deletion copy number variants involving *FOXF1* or its 60-kb tissue-specific enhancer region mapping 270 kb upstream of *FOXF1* and involving fetal lung-expressed long non-coding RNA genes and CpG-enriched sites on chromosome 16q24.1

• 141 families studies, have 86 pathogenic variants in the *FOXF1* locus: 38 deletion CNVs, one complex rearrangement and 47 point mutations
CONCLUSIONS

• Postmortem examination:
  • Determine the cause of death is just one of the goals of perinatal autopsy
    • Quality of Medical Care
    • Unexpected findings with possible implication for the family
    • Unidentified infection
    • Clarification of the clinical differential diagnosis