Analytical Literature Review of Cleft Lip and Palate

Roshni Biswas
Vivian Tao
Partner for Surgery
lives transformed through medical care
Surgical Care

Milken Institute School of Public Health
THE GEORGE WASHINGTON UNIVERSITY
Partner for Surgery

- Incorporated in May 2001
- Mission: “To connect patients in need of surgical care in remote communities with the international volunteer triage and surgical teams that traveled to Guatemala, and to educate and empower rural Guatemalans to initiate and advocate for vital health care services on their own behalf.”
- Surgical care in the most remote areas of Guatemala
- Guatemala-based partner
  - Asociación Compañero Para Cirugía
- Cleft Infant Nutrition Program (CINP)

Source: partnerforsurgery.org/
BACKGROUND

• Development of Cleft Lip and Palate
  – Left and right sides of the facial skeleton fuse in the midline between the 6th and 12th weeks of fetal gestation
  – Failure to fuse: Craniofacial cleft
  – Various types of clefts may occur
    • Isolated condition (Non-Syndromic)
    • Part of a syndrome ( Syndromic)
BACKGROUND (cont…)

• Statistics
  – 1 in 700 children
  – Average prevalence:
    7.75 per 10,000 live births in the United States
    7.94 per 10,000 live births globally
  – Alta Verapaz, Rural North-Central Guatemala
    1-year prevalence rate of:
    18.9 per 10,000 for cleft lip
    4.7 per 10,000 for cleft palate
  -Males: Females- 2:1
  -Left-sided: Right-sided- 2:1
### Prevalence of Cleft lip with or without cleft palate—Top 10

<table>
<thead>
<tr>
<th>Programme</th>
<th>Years from</th>
<th>Years to</th>
<th>Cases</th>
<th>Births</th>
<th>Rate per 10 000</th>
<th>95% CI* lower</th>
<th>95% CI* upper</th>
<th>Trend</th>
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</thead>
<tbody>
<tr>
<td>Bolivia</td>
<td>93</td>
<td>98</td>
<td>78</td>
<td>34 007</td>
<td>22.94</td>
<td>18.13</td>
<td>28.62</td>
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<tr>
<td>Japan — JAOG</td>
<td>93</td>
<td>98</td>
<td>993</td>
<td>619 107</td>
<td>16.04</td>
<td>15.06</td>
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<tr>
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<td>16 108</td>
<td>14.90</td>
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<td>22.17</td>
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<td>Germany — Saxony-Anhalt</td>
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<td>98</td>
<td>71</td>
<td>50 947</td>
<td>13.94</td>
<td>10.88</td>
<td>17.58</td>
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<tr>
<td>China — CBDMN</td>
<td>97</td>
<td>98</td>
<td>814</td>
<td>598 316</td>
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<td>12.69</td>
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<tr>
<td>Northern Netherlands</td>
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<td>98</td>
<td>157</td>
<td>116 337</td>
<td>13.50</td>
<td>11.47</td>
<td>15.78</td>
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<tr>
<td>Norway</td>
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<td>483</td>
<td>360 906</td>
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<td>12.22</td>
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<tr>
<td>Denmark — Odense</td>
<td>93</td>
<td>98</td>
<td>46</td>
<td>35 285</td>
<td>13.04</td>
<td>9.54</td>
<td>17.39</td>
<td></td>
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<tr>
<td>Mexico — RYVEMCE</td>
<td>93</td>
<td>98</td>
<td>369</td>
<td>294 380</td>
<td>12.53</td>
<td>11.29</td>
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<tr>
<td>Argentina</td>
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<td>509</td>
<td>412 862</td>
<td>12.33</td>
<td>11.28</td>
<td>13.45</td>
<td></td>
</tr>
</tbody>
</table>

Global map of prevalence of cleft lip with or without cleft palate. Rates per 10,000. Shaded by quartiles of rates:

- Light pink: 3.37 - 6.26
- Light orange: 6.27 - 7.83
- Medium orange: 7.84 - 10.58
- Dark orange: 10.59 - 22.94

Genetics

- 50% cases- Non-syndromic CLP
- Genetic association seen in Non-syndromic CLP
- Higher frequency of CL/CP in individuals of Asian, African, and Native American descent
- Oligogenic model of inheritance-One or few genes are influenced by modifiers
- Genes and loci involved: IRF6 (association seen in multiple studies), VAX1, 8q24, 22q11 deletion
- Most isolated cases have CLP gene and environment interaction
- Type of cleft is consistent in families; severity is not
## Genetics (cont…)

### Table 1: Risks for recurrence associated with isolated CL/CP and CP (5)

<table>
<thead>
<tr>
<th></th>
<th>CL/CP (%)</th>
<th>CP (%)</th>
</tr>
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<tbody>
<tr>
<td>General population</td>
<td>0.1</td>
<td>0.04</td>
</tr>
<tr>
<td>1 affected sibling</td>
<td>3-7</td>
<td>2-5</td>
</tr>
<tr>
<td>1 affected parent</td>
<td>2-4</td>
<td>3-7</td>
</tr>
<tr>
<td>1 affected parent and 1</td>
<td>11-14</td>
<td>15-20</td>
</tr>
<tr>
<td>affected sibling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 affected siblings</td>
<td>8-14</td>
<td>10-13</td>
</tr>
</tbody>
</table>
Genetics—continued

- Consanguinity (Intermarriage)
  - Definition: Marriage between close relatives (first-cousin)
  - Common in less developed area due to
    - 1) the remoteness of the location and
    - 2) religious reasons and cultural preferences.
  - Children have doubled risk of genetic disorders (6% vs 3%)
  - Occurrence of CL/P in offspring is consistently higher
Maternal Diseases

- High maternal age and high paternal age
  - 15-20% increased risk per 10-year increase in age.
- Obesity prior to and during pregnancy
- Uncontrolled or poorly controlled diabetes
  - Both obese and diabetic mothers: x3 times more
- Maternal hypertension
- First trimester maternal influenza
- Others: genital tract infections, orofacial herpes, and gastroenteritis during pregnancy; chronic maternal disease such as epilepsy and angina pectoris
Maternal infection and Drug use

- Prenatal exposure to antiepileptic drugs - Valproate and phenobarbital
- Topiramate-higher in the first trimester of pregnancy
- Dose dependent increase
- Increased the risk of a cleft lip, with or without a cleft palate, but not the risk of a cleft palate alone
- Mechanism of action of anti-epileptics- Folate inhibitors
- Unlike other folate inhibitors- Maternal supplementation with multivitamins containing folic acid was not associated with a diminution in the risk of oral clefts
- Amoxicillin use in first trimester increases risk
Environmental Factors
• Caused by an interaction of genetic and environmental factors
  1) Inherit genetic information from parents-make certain offspring more likely to develop cleft lip and cleft palate
  2) Then exposures to certain environmental triggers during pregnancy actually cause the cleft lip to occur

• Genetic contribution to the development of cleft lip and palate falls between 20%-50% and the rest is attributed to environmental factors and gene-environment interaction
Smoking

• Smoking during pregnancy exposes the fetus to
  – lead, cyanide, and other known carcinogens
• Women who smoke during pregnancy - increased risk
  – Confounding factors - maternal race, age, and educational level
  – Women who smoked anytime during the first trimester - fetus at a higher risk
  – Second hand smoking during pregnancy associated with an increased risk
• Dose-response relationship
• Presence of specific cleft-prone gene can be aggravated by smoking
Occupational Hazards

- Maternal occupational exposure to organic solvents, glycol ethers and pesticides increases risk
- Women working in leather industry and hairdressers are shown to have an increased risk
- Evidence is very limited
Socioeconomic Status (SES)

- Low socioeconomic status
- Live in a rural area
- Born at home or in a publicly funded hospital
- Lowest household SES index had the strongest association with birth defects
- Association with parental education level and type of occupation
Nutrition- Folic Acid

- Folic acid – most important nutritional factor
- Folic acid supplements during early pregnancy reduce the risk of isolated cleft lip (with or without cleft palate) by about a third
• Effectiveness of CLP prevention restricted to early stages of embryogenesis
• Folate supplementation given to women of reproductive age, or at least three months before pregnancy and during the first trimester of pregnancy
• Occurrence of CLP reduced by prophylactic use of folate in the periconceptional period
• Reasons for failure in folate supplementation:
  – Unplanned pregnancy
  – Advised only to pregnant women
Fungus-Fumonisins

- Fumonisins - family of mycotoxins produced by the fungus Fusarium verticilloides
- Found in maize and corn
- Increased incidences - populations where maize and corn are a part of the staple diet
- Mouse studies - fumonisins interfere with the functions folate binding proteins - interfere with folate utilization
- Folate supplementation reduces the incidence
- Guatemala population - fumonisins and aflatoxins largely found in the diet (maize) and increased prevalence of orofacial clefts
CONCLUSIONS

• Develops in early part of pregnancy
• Multiple factors are responsible
• Genetic association significant-differences by race and gender
• Interaction between genetic and environmental factors
• Folic acid is the most important factor
RECOMMENDATIONS

• Reducing smoking and occupational hazards
• Opting for alternative drugs; dose adjustment
• Adequate treatment of infection
• Preventive interventions targeted to periconceptional and early pregnancy period
• Increase intake of multivitamin and folic acid
• Strategies:
  - Advising folic acid to all women of reproductive age group.
  - Folic acid supplementation
QUESTIONS?
THANK YOU!