GROWTH DEFICIENCY IN CYSTIC FIBROSIS IS OBSERVABLE AT BIRTH AND PREDICTIVE OF EARLY PULMONARY FUNCTION

by
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Conflict of Interest Disclosures
In relation to this presentation, I declare that there are no conflicts of interest.

Cystic Fibrosis

- Autosomal recessive genetic disease
- 1:3,500 Caucasian births and an estimated 30,000 people in the United States.
- Average lifespan of a patient with CF to 37.8 years.
CFTR

- Caused by mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR)
- 7q31.2, and is composed of 27 exons spanning approximately 250 kb
- 86.7% of patients have one or two ΔF508 mutations

Phenotypic Manifestations in CF

- Multi-organ disease
  - Nose
  - Esophagus
  - Heart
  - Lungs
  - Liver
  - Gallbladder
  - Intestinal tract
  - Lungs
  - Spleen
  - Spleen
  - Pancreas
  - Reproductive tracts
  - Bone
  - Sweat glands

Growth Deficiency in CF


Cystic Fibrosis Foundation Patient Report, 2012
Growth Deficiency in CF

- Lower caloric intake
- Higher energy expenditure
- Malabsorption

Haller et al., 2014

Babies with CF are Significantly Smaller at Birth

- Study in Tuscany, Italy
  - On average 246.2 g (8.7 oz) lighter (P= 0.0003)
  - Full term: 205.7 g (7.25 oz) lighter (P= 0.0002)

Weight at Age 4 Correlates with Pulmonary Function in CF

- Yen, Quinton, and Borowitz (2012)
Research Question

- Correlation between growth and pulmonary function in patients with CF
- Growth deficiency in CF has been observed at birth

Is there a correlation between birth weight and the severity of medical complications associated with cystic fibrosis?

Aim 1

- Determine the mean birth weights of patients with CF and compare these birth weights to national averages matched for gender

Babies with CF Weigh Significantly Less than the National Averages
Birth Weight Does Not Differ by Gender

![Graph showing birth weight by gender.](chart)

**Birth Weight (g)**

<table>
<thead>
<tr>
<th>Birth Weight (g)</th>
<th>Males (n=40)</th>
<th>Females (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2700</td>
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<tr>
<td>2900</td>
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<td>3100</td>
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<tr>
<td>3500</td>
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</tr>
</tbody>
</table>

**p=0.28**

Birth Weight in CF Does Not Differ by Year of Birth

![Graph showing birth weight by year of birth.](chart)

**Birth Weight (g)**

<table>
<thead>
<tr>
<th>Birth Weight (g)</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2500</td>
<td>0-5</td>
</tr>
<tr>
<td>2700</td>
<td>6-10</td>
</tr>
<tr>
<td>2900</td>
<td>11-15</td>
</tr>
<tr>
<td>3100</td>
<td>16-20</td>
</tr>
<tr>
<td>3300</td>
<td>21-25</td>
</tr>
<tr>
<td>3500</td>
<td>≥26</td>
</tr>
</tbody>
</table>

**ANOVA: p=0.424**

Birth Weight in CF Does Not Differ by Genotype

![Graph showing birth weight by genotype.](chart)

**Birth Weight (g)**

<table>
<thead>
<tr>
<th>Birth Weight (g)</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>2500</td>
<td>∆F508 Homozygous (n=48)</td>
</tr>
<tr>
<td>2700</td>
<td>∆F508 Heterozygous (n=31)</td>
</tr>
</tbody>
</table>

**p=0.24**
Birth Weight in CF Does Not Differ By Presence of Meconium Ileus

<table>
<thead>
<tr>
<th>Birth Weight (g)</th>
<th>MI (n=28)</th>
<th>No MI (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2500</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2700</td>
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<tr>
<td>3500</td>
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</tr>
</tbody>
</table>

Summary of Findings

- Patients with CF have significantly lower birth weights than the national average, matched for gender.
- Gender, age, genotype, and presence of MI do not contribute to any significant difference in birth weight.

Aim 2

- Determine if there is a correlation between birth weight and variability of clinical phenotype of patients with CF.
FEV\textsubscript{1} % and Birth Weight

Birth Weight in CF Contributes to 8% of the Variance of Pulmonary Function at Age 6

\[ b=0.01 \]
\[ R^2=0.08 \]
\[ p=0.04 \]

Birth Weight in CF Contributes to 7% of the Variance of Pulmonary Function at Age 10

\[ b=0.01 \]
\[ R^2=0.07 \]
\[ p=0.05 \]
Birth Weight is not Correlated with FEV$_1$% at age 15

$n=45 \ p=.93$

Birth Weight is not Correlated with FEV$_1$% at age 20

$n=17 \ p=.683$

Overall FEV$_1$% by age
Summary Slide

- Growth deficiency in CF is observable at birth
- Gender, year of birth, genotype, and MI are not associated with birth weight in patients with CF
- Birth weight is associated with pulmonary function at age 6, and trends towards association at age 10
- No association is observed at ages 15 and 20

Percent Ideal Body Weight

Nutritional Status | %IBW
--- | ---
Morbidly obese | ≥200
Obese | 120-199
Overweight | 110-120
Normal | 90-109
Mild malnutrition | 80-89
Moderate malnutrition | 70-79
Severe malnutrition | ≤70

Original %IBW over the ages

Summary Slide

- Growth deficiency in CF is observable at birth
- Gender, year of birth, genotype, and MI are not associated with birth weight in patients with CF
- Birth weight is associated with FEV₁ % at ages 6 and 10, but not at age 15 and 20
- Birth weight trends towards association with %IBW at ages 6 and 10
- No association is observed at ages 15

Meconium Ileus and %IBW in CF

Birth Weight is Only Associated With %IBW at Age 6 in Patients Born Without MI

\[ R^2 = 0.004, \ p = 0.74, \ n = 28 \]

\[ R^2 = 0.229, \ p < 0.01, \ n = 30 \]
Birth Weight Only Trends Towards Association With %IBW at Age 10 in Patients Born Without MI

<table>
<thead>
<tr>
<th>With Meconium Ileus</th>
<th>Without Meconium Ileus</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

$R^2 = 0.039, p = 0.37, n = 24$

$R^2 = 0.106, p = 0.08, n = 35$

Birth Weight Only Trends Towards Association With %IBW at Age 15 in Patients Born Without MI

<table>
<thead>
<tr>
<th>With Meconium Ileus</th>
<th>Without Meconium Ileus</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3.png" alt="Graph" /></td>
<td><img src="image4.png" alt="Graph" /></td>
</tr>
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</table>

$R^2 = 0.019, p = 0.64, n = 14$

$R^2 = 0.106, p = 0.08, n = 31$

Summary Slide

- Growth deficiency in CF is observable at birth
- Gender, year of birth, genotype, and MI are not associated with birth weight in patients with CF
- Birth weight is associated with FEV1% at ages 6 and 10, but not at age 15 and 20
- In patients born without MI, birth weight is associated with %IBW at age 6 and trends towards association at ages 10 and 15
- No association is observed at ages 15
No Difference in the Birth Weights of Patients With And Without \textit{Pseudomonas} Colonization

\[ p = 0.93 \]

No Difference in Birth Weight of Patients with CFRD and Adult Patients Without CFRD

\[ p = 0.13 \]

In Patients With CFRD, Birth Weight Contributes to 26\% of the Variability in Age of CFRD Diagnosis

\[ R^2 = 0.26, p = 0.04. \]
Summary Slide

- Growth deficiency in CF is observable at birth
- Gender, year of birth, genotype, and MI are not associated with birth weight in patients with CF
- Birth weight is associated with FEV\(1\)\% at ages 6 and 10, but not at age 15 and 20
- In patients born without MI, birth weight is associated with %IBW at age 6 and trends towards association at ages 10 and 15
- Age of Pseudomonas colonization is not associated with birth weight in patients with CF
- No difference between birth weights of patients with CFRD and adult patients without CFRD
- In patients with CFRD, birth weight is positively correlated with age of CFRD diagnosis

Conclusions: Aim 1

- Growth deficiency in patients with CF is observable at birth
  - Males were 290.4 g (10.24 oz) lighter than national average
  - Females were 256.25 g (9.04 oz) lighter than the national average
- No significant difference between sex, genotype, current age, meconium ileus

Growth Deficiency in CF

- Lower caloric intake
- Higher energy expenditure
- Malabsorption

Haller et al., 2014
Conclusions Aim 2

- Early pulmonary function is correlated with birth weight
  - As patients age, additional factors become more important than birth weight
- In patients born without MI, nutritional status is correlated with birth weight
  - Before newborn screening, patients without MI may not have been diagnosed with CF at birth may have not received early treatments
  - Patients with MI receive more aggressive nutritional treatment early on in life

Additional morbidities of CF

- Pseudomonas colonization
  - No difference between birth weight and those with early colonization vs those with no colonization.
- CFRD
  - No difference between birth weights of those with CFRD and adults without CFRD.
  - In patients with CFRD, birth weight is positively correlated with age of CFRD diagnosis

Clinical Implications

- Growth deficiency
  - Additional factors may be causing growth deficiency prenatally, could they also cause growth deficiency in childhood and adulthood?
- Birth weight is the first indicator of pulmonary function in early childhood
- Early CF diagnosis or early nutritional intervention influence nutritional status
Significance for Genetic Counseling

- Birth weight as an early predictor for pulmonary function and nutritional status.
  - Early intervention (pre or postnatally)
- Increase the specificity of NBS by including birth weight into the calculation
- Birth weight is not the be all end all
  - Encourage patients, parents, and clinicians to focus on increasing the patient’s weight.

Limitations

- Self-reported birth weights
- Response bias
  - Young study population
  - Patients who have more serious complications were more likely to be seen in the CFC
- Small population
- Retrospective cross-sectional study design

Future Directions

- Future research into the cause of low birth weight
  - Placental function
  - Looking at growth hormones in fetuses with CF
- Larger study population with older patients
- Use of birth weight as an indicator of early aggressive treatment
- Correlation between birth weight and %IBW in a population without an early diagnosis bias for patients with MI
Acknowledgements

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- Anne Matthews

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Questions?