HORMONAL REVENGE: GROWTH AND PUBERTY IN THE INTERNATIONALLY ADOPTED CHILD

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Disclosure

• Dr Mason is the Medical Director of Endocrinology for Quest Diagnostics Nichols Institute

• Nothing presented today will be related to his work at Quest
• There are no other disclosures

Objectives- What should you get out of the lecture?

• Understand the phenomenon of growth delay and early puberty in the Internationally adopted child
• Discuss the evaluation and treatment options for early puberty

A Case

• Adopted at age 3 years
• At adoption “well below the curve” for height
• At age 7 years height at the 50 %tile
• Showing signs of early puberty

Question: Are many adopted children short and are they at risk for early puberty?

Growth in the Post-Institutionalized Child

• Johnson et al* (JAMA, 1992) decrease in height, weight, and head circumference with institutionalization
  • Loss of 1 month of height for each--
    – 2.6 months in Romanian/Bulgarian Orphanage
    – 3 months in a Chinese Orphanage
    – 3.4 months in a Russian Orphanage
• Miller & Hendrie (Ped 2000) 192 children from China
  – Lost 1 month of height for each 2.86 months in orphanage
Growth Measurements for Internationally Adopted Children

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight Z-score</th>
<th>Height Z-score</th>
<th>Head Circumference Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romania, N=65 (Johnson et al, 1992)</td>
<td>-1.10</td>
<td>-1.68</td>
<td>-1.06</td>
</tr>
<tr>
<td>22 countries, N = 129 (Miller et al, 1995)</td>
<td>-0.76</td>
<td>-1.36</td>
<td>-1.03</td>
</tr>
<tr>
<td>Russia, N = 210 (Johnson et al, 1996)</td>
<td>-1.71</td>
<td>-2.09</td>
<td>-1.15</td>
</tr>
<tr>
<td>Eastern Europe, N=56 (Albers et al, 1997)</td>
<td>-1.05</td>
<td>-1.41</td>
<td>-1.25</td>
</tr>
<tr>
<td>N=42 (Rutter et al, 1998)</td>
<td>-2.20</td>
<td>-2.30</td>
<td>-2.20</td>
</tr>
<tr>
<td>China, N = 192 (Miller et al, 2000)</td>
<td>-1.17</td>
<td>-1.51</td>
<td>-1.43</td>
</tr>
<tr>
<td>Guatemala, N=50 (Miller et al 2005)</td>
<td>-1.00</td>
<td>-1.04</td>
<td>-1.08</td>
</tr>
<tr>
<td>Eastern Europe, N=138 (Miller et al 2009)</td>
<td>-1.43</td>
<td>-1.23</td>
<td>-0.63</td>
</tr>
<tr>
<td>Mixed N=289 (Palacios et al 2010)</td>
<td>-1.48</td>
<td>-1.46</td>
<td>-0.71</td>
</tr>
</tbody>
</table>

Summary of Growth in the Internationally Adopted Child

- Children currently adopted into the US have growth stunting on arrival
- What might cause the observed poor growth?

Why do Post-Institutionalized Children Not Grow?

- Likely multi-factorial
  - poor nutrition
  - environmental pollutants
  - genetics and genetic syndromes
  - medical syndromes and complications
  - prematurity, IUGR
  - “psychosocial” factors
  - STRESS?

What do we know about stress and growth?

- Human and animal studies show cortisol (the body's stress hormone) inhibits growth hormone
- Animals in abusive environments have elevated “stress hormone” levels and poor growth.
- Children in abusive, neglectful families have reversible GH deficiency (psychosocial short stature)
- Are the children coming from a STRESSFUL environment?
Where do the Children Come From? Foster to Institutional Care

<table>
<thead>
<tr>
<th>Year</th>
<th>Foster Care</th>
<th>Institutional Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>38%</td>
<td>62%</td>
</tr>
<tr>
<td>2000</td>
<td>82%</td>
<td>18%</td>
</tr>
</tbody>
</table>

International Adoption: “Children at Risk”

- Adopted children are different due to their “stressful” backgrounds
  - poor prenatal conditions
    - genetics, prenatal exposures
  - Greater birth problems
    - home deliveries, lack of prenatal care, prematurity
  - Poor social conditions
    - poverty, abuse, abandonment, physical deformities

- Poor orphanage environment
  - High child-caregiver ratio, lack of food and medical care, lack of consistent caretakers

What does an orphanage look like?

- A high child to caregiver ratio
- Children often left on their own without supervision
- Lack of consistent caregivers
- Meals often poor in nutrition and very regimented in timing
Many children get little stimulation.

Children generally have few possessions and little stimulation. There is generally little education.

Caregivers are not trained in child development and have a high turnover rate.

Romanian Growth Project 1999-2000

Growth Stunting in Romanian Orphanages

Boys (n=57) Girls (n=83)
Correlation of IGF-I and Height

\[ r = 0.59 \quad p < 0.001 \]

Are the Children Stressed?
Mean Peak Cortisol Values

Predictors of Growth Stunting
Multivariate Relationship with Growth

<table>
<thead>
<tr>
<th>Variable</th>
<th>r-value</th>
<th>% of total variance</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I</td>
<td>0.6</td>
<td>34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cortisol</td>
<td>-0.187</td>
<td>4</td>
<td>0.029</td>
</tr>
<tr>
<td>% of time in Orphanage</td>
<td>-0.187</td>
<td>4</td>
<td>0.030</td>
</tr>
<tr>
<td>Total of 3 Variables</td>
<td>0.65</td>
<td>42</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Summary

- Children living in an orphanage have significant growth stunting
- Much of the growth stunting (42%) can be predicted by
  - Percentage of time within the orphanage,
  - Cortisol values
  - IGF-I levels
- Suggests a relationship between the environment, the child’s level of stress and growth hormone.
- Further studies are needed to help confirm the impact of the HPA “stress” response on growth.
- What happens after the adoption?

Catch-up Growth

- Most studies show catch-up in growth after their adoption
- Marked increase in height velocity during catch-up growth (mean z-score of +5.5)
- Most children show improvement in growth within 6 months post-adoption
- Work-up may not be needed within first 6-8 months
- Persistent poor growth should be evaluated
Growth Failure and Catch-up
The Emory Survey

On arrival growth analysis

- Examined 138 children soon after arrival
  - Mean age 20.4 months
  - Time in US 17 days, Time in orphanage 17 months
- Growth parameters all small
  - Ht SDS -1.23, Wt SDS -1.43
- Hormonal growth markers low
  - IGF-I -1.04, IGFBP-3 -0.9
- Linear regression for Height showed correlation with
  - Age, low birth weight, IGFBP-3 and markers of FAS

Growth Catch-up Study

Catch up growth

Summary of Growth in the Internationally Adopted Child

- Children adopted into the US have growth stunting on arrival
- Most children show “catch-up growth” after their adoption

Does the increased growth come at a price?

Hormonal Revenge: Effect of Institutionalization on Puberty
Precocious Puberty in the Internationally Adopted Child

- Adolfsson and Westphal* - 7 girls from India and Bangladesh
  - Small at arrival (-2.1 SD) and catch-up growth (3.2SD)
  - All had early puberty, with 4 with periods by age 7.6 years
- Proos et al* 107 Indian girls adopted into Sweden
  - Median menarcheal age 11.6 (range 7.3-14.6)
  - Higher SEC (12.4-12.9) Lower SEC (13.7-14.6)
  - Swedish controls (13.7-14.4)
- Association of menarcheal age and height at adoption and extent of catch-up growth

Emory Survey Results

Puberty

- 193 girls.
- 30% had some evidence of puberty
- Breast Development - mean age 8.8 ± 2.5
  - (30% of females - 57 of 193)
- Pubic Hair - mean age 9.1 ± 2.3
  - (28% of females - 54 of 193)
- Menarche - mean age 10.5 ± 2.6
  - (12% of females - 23 of 193 plus 7 on Lupron)

What’s normal for puberty?

When Should Puberty Occur?

- Evaluate Growth and Tanner Stage
- Determine Bone Age
- Laboratory Studies
  - Sex steroid levels
  - GnRH stimulation test
- Ultrasound- Abdomen and Pelvis
- Other studies determined by level of suspicion

Evaluation of Precocious Puberty

Puberty in the Adopted Child

- Virdis et al 1998 - 19 adopted girls referred for IPP
  - All demonstrated signs of early puberty
    - Breast starting at age 6.9 years
  - Bone age progressed rapidly, puberty was completed faster and girls were overall shorter
- Baron et al 2000 - 10 girls, 3 boys
  - All had increased growth rate upon arrival and early puberty
  - Surveyed 99 families in France
    - 44.9% girls showed early puberty, only 8.6% of boys
    - Thought to be related to growth and nutritional catch-up
Management of Central Precocious Puberty

• Pharmacological - GnRH Agonists
  – GnRH Agonists eliminate pulsatility
  – Depot Lupron, 3.75 to 11.25 mg im Q4wks
  – Histrelin Implant (Supprelin LA) good for 1 year
  – Desensitizes the HPG Axis
  – Does not impede Adrenal Androgen Production

Follow-Up Evaluation of Therapy

• Need to repeat the exam, GnRH stimulation test and sex steroid levels to insure suppression
• For Lupron Therapy
  – Slowly increase the dose as needed to fully suppress the gonadal axis
  – Continue therapy every 4 weeks
• When to stop?

Should you intervene?

• Why would you intervene?
  – Impact on final adult height
  – Social and emotional development
• What can you do?
  – Do nothing?
  – Watch for signs of rapidly developing puberty?
  – Offer hormonal treatment?
    • GnRH agonist?
    • GnRH plus Growth hormone?

Summary of Research on Growth and Puberty

• Children adopted from orphanages are smaller and weigh less at the time of adoption.
• They may show “catch-up” growth but this decreases with duration of institutionalization
• At increased risk for early and rapidly progressing puberty which may be related to the extent of catch-up growth
• When and how to treat still controversial

Conclusion

• Adopted children at risk for a wide variety of health and developmental problems
• Initial growth failure followed by “catch-up” growth
• Girls at risk for early puberty
• Growth failure may be influenced by the HPA “stress” axis
• Further studies needed to explore the influences of early life experiences on subsequent growth

Post Adoption Evaluation?
Post-Adoption Medical Evaluation

• Thorough History
  – Past history
  – Family background

• Complete medical and developmental evaluation.
  – Often look good physically but delayed developmentally

Laboratory studies:
- Complete blood count
- HIV 1 and 2
- Syphilis (both treponemal and non-treponemal)
- PPD
- Stool for O & P X 3
- Stool for Giardia and Cryptosporidium antigen

Red Book 2009, pg 177-184

Also recommend Thyroid, Lead, Hearing and vision screening.

Tuberculosis Screen

• Saiman, Aronson et al Peds 2001
  – 19% (75) had positive TST

• Johnson et al AAP 2004
  – Children who received BCG were significantly less likely to be screened with TST

• Current Red Book recommendations
  – “Receipt of BCG vaccine is not a contraindication to a TST, and a positive TST result should not be attributed to BCG vaccine”. Red Book, 2009 p181

Immunizations

Reliability of Immunization Records

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Titer</th>
<th>Total Pt</th>
<th>Positive titers</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTP</td>
<td></td>
<td>147</td>
<td>146 (99.3)</td>
</tr>
<tr>
<td>Tetanus</td>
<td></td>
<td>142</td>
<td>125 (88)</td>
</tr>
<tr>
<td>Polio 1,2,3</td>
<td></td>
<td>150</td>
<td>142 (94.7)</td>
</tr>
<tr>
<td>Hep B</td>
<td>HepBsAb</td>
<td>160</td>
<td>131 (81.9)</td>
</tr>
<tr>
<td>Measles</td>
<td>Measles</td>
<td>62</td>
<td>57 (91.9)</td>
</tr>
<tr>
<td>Mumps</td>
<td>Mumps</td>
<td>48</td>
<td>32 (66.7)</td>
</tr>
<tr>
<td>Rubella</td>
<td>Rubella</td>
<td>25</td>
<td>23 (92)</td>
</tr>
</tbody>
</table>

Crouch et al. AAP 2006

Other New Recommendations

• Hepatitis A Vaccine in Close Contacts of Newly Arriving International Adoptees
  – MMWR Sept 18, 2009/58(36);1006-1007
  – 2007 – 21 cases of acute hep A among persons who had close personal contact w/ newly arriving intl adoptees and no h/o traveling abroad.
  – 2008 – 14 additional reports

What to do about Immunizations?

Need to evaluate the immunization status

Red Book:
- If dates and records complete titers vs continue
- Schulte et al, Peds 2002 65% no records
- Children > 6months check D and/or T titers
- Children >12 months can add M, M, R and varicella
- Plus Hepatitis B series

Red Book 2006, pg 187-188
**Developmental Delays in the Post Adopted Child**

N = 129  

Why would there be delays?

• “Time use” study within the orphanage  
  – Followed 138 non-special needs children (age 1 month to 4 years)  
  – Evaluated every 10 minutes for 5 hours  

• Children 50% of their time alone, 27% with caregiver, 15% with another adult, 7% with another child  

• Time alone  
  – Infants (65%), toddlers (43%), preschoolers (46%)

Miller et al,Arch Ped Adol Med 1995, 149:40-44
Miller and Hendrie, Peds, 2000, e76

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**Health, Growth, Development and Maternal Histories of children in Russian Orphanages**

• Chart review of 193 children in an orphanage in Russia (age range 2-72 months)  

• Maternal history  
  – Chronic illness 45%  
  – Alcohol 39%  
  – Tobacco 41%  
  – Illicit drugs 7%  

• At entry into baby home  
  – 34% had weight z-score <-2  
  – 25% had length z-score <-2  
  – 34% had head circumference z-score <-2  

Miller et al, AAP 2006

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**Risk of Alcohol Exposure**

• Assessment of newly adopted children – part of larger growth and stress study (U of Minn and Inova)  

• Enrolled children age 1-4 yrs from Russia  
  – Screen for facial features of FAS (U of Wash)  
  – Measure growth markers and cortisol levels  

• High risk/ FAS facial features – 15%  
  – 66.7% below -2 SD for height vs 27% with normal facial features  

• High rate of FAS exposure for children from Russia  

Korajkina et al, AAP 2006

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**Long-term Developmental Changes-10 years post placement**

• 35% significantly improved  

• 35% few serious problems but progressing  

• 30% several serious problems  
  – IQ< 85, Atypical attachment, Severe behavior, stereotypical behavior


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**Health, Growth, Development and Maternal Histories of children in Russian Orphanages**

• Developmental levels within the orphanage  
  – Normal levels 32%  
  – Mild delay 11%  
  – Moderate delay 25%  
  – Severe delay 28%  

• Developmental level strongly correlated with growth  

Miller et al, AAP 2006
Comparison of Development for Children
Adopted from Russia, China and Guatemala

• Reviewed 168 medical records for children seen <1 month and 3-6 month post adoption
• Followed up phone survey 1-3 years post adoption
• Initial expressive speech delay
  – Russia -6.4 months
  – China -4.5 months
  – Guatemala -2.4 months
• No significant differences seen between populations in long-term follow-up

Mason et al, PAS 2007

Speech and Language

• Speech delays are the most common and consistent developmental delay in adopted children
• Our survey 35% had speech delay and 60% seen by speech therapist
• When should children catch-up and when should you be concerned?

Language Delays

• Evaluated children adopted 12-24 month and back 2-3 months
  – 18% were below threshold on Communication and Symbolic Behavioral Scales (CSBS-DP)
• Reevaluated at 1, 2 and 3 years post adoption
  – 80% of those delayed at 3 months were still delayed.
• Our study (Harmelin & Mason 2009 PAS)
  – Screened 106 children at adoption and 3 months later
  – 64% of children failed to show catch-up 3 months post adoption

What about the parents?

• 39 Israeli women examined for depression and other psychopathologies pre and post adoption
• Surveyed women before their adoption and 6 weeks after the adoption.
• Pre adoption
  – No difference in depression from general population (25.6% vs 26%)

Senecky et al J Affective Disorder 2009
Post Adoption Depression

• Post adoption
  – No difference in depression compared to birth mothers (15.4% vs 15%)
  – All women with depression after the adoption were also depressed before the adoption
• Post adoption depression correlated with
  – length of time between pre and post adoption measurements
  – marital status
  – ordinal status of the adopted child
  – maternal age

Senecky et al J Affective Disorder 2009

What about the parents?

• Online Stress survey of parents
• 122 parents surveyed
  – 90 mothers, 32 fathers.
  – 16 couples
• Surveyed on-line with demographic questions and Parent Stress Index

Highly Stressed Parents
(≥ 85th Percentile)

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 122)</th>
<th>Men (n = 30)</th>
<th>Women (n = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Stress (TS)</td>
<td>43.4%</td>
<td>50%</td>
<td>41.3%</td>
</tr>
<tr>
<td>Parent Domain (PD)</td>
<td>39.3%</td>
<td>46.7%</td>
<td>37%</td>
</tr>
<tr>
<td>Child Domain (CD)</td>
<td>35.2%</td>
<td>36.6%</td>
<td>34.8%</td>
</tr>
<tr>
<td>Life Stress (LS)</td>
<td>17.2%</td>
<td>16.6%</td>
<td>17.4%</td>
</tr>
</tbody>
</table>

Discussion

• Internationally adoptive parents do experience stress
• Gender differences were not found to be significant in this sample
• Parents with children home 2-4 years were more likely to be highly stressed
• Highly stressed parents were more likely to have older children at the time of the survey
• Non-significant trend in demandingness and depression