Growth retardation in early onset IBD: should we monitor and treat these patients differently?

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Outline

- Defining and recognizing impaired growth
- Prevalence of growth impairment in paediatric IBD
- Understanding pathophysiology as key to prevention
- Prevention and management of growth retardation in current era of treatment
What is normal growth?
Assessing growth: Centiles and Standard deviation (Z) scores

- At any age height is distributed in a roughly “normal” manner

- **z score**
  - Relative distance away from the mean
  - **z score of 1 is equal to 1 SD away from the mean**
Recognizing growth impairment: definitions

For populations
- Mean Z score height

For individuals
- Change in Z score for height between 2 time points (e.g., from pre-illness to diagnosis)
- Height velocity (cm/year or Z score)
Recognition of growth retardation: Illustrative case

- 8 year old boy: unwell for 3 months

- Diarrhea (4-6/day; 2-3/night), some blood dripping with stools; abdominal pain; fevers; mouth sores; weight loss 11 lbs over 3 months; off school

- Prior history of chronic recurring iron deficiency anemia (Hb 72 MCV 66) at beginning at age 5 years (negative celiac serology); on and off loose stools
Investigations

- Hb 100, MCV 70; Albumin 28 mg/dl; ESR 50

- Colonoscopic findings: perianal disease (erythema, tags, fissure)

- Relatively normal rectum; otherwise edematous, friable mucosa throughout colon

- Ulcerated and inflamed terminal Ileum
Prevalence of Growth Impairment in IBD

- Uncommon in UC

- Historically common in CD
  - Prior to diagnosis
  - During follow-up (despite treatment)
  - At maturity
# Height at diagnosis reflects growth prior to diagnosis: Crohn disease

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Patients</th>
<th>Z score for height (SD)</th>
<th>Z score &lt; ~ -2.0 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toronto 1990-99</td>
<td>Tanner I/II (n=161)</td>
<td>-0.74 (1.2)</td>
<td>22%</td>
</tr>
<tr>
<td>UK 1998-99 Surveillance</td>
<td>Age &lt; 16 yrs (n=333)</td>
<td>-0.54 (1.3)</td>
<td>13%</td>
</tr>
<tr>
<td>Israel 1991-2003</td>
<td>Age &lt;18 years (n=93)</td>
<td>-0.56 (1.2)</td>
<td>20%</td>
</tr>
<tr>
<td>Toronto 2001-2009</td>
<td>Tanner I/II (n=202)</td>
<td>-0.43 (1.1)</td>
<td>7%</td>
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Kundhal 2002; Sawczenko 2003; Wine 2004; Walters 2009
## Height at diagnosis: Ulcerative colitis

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<th>Cohort</th>
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<th>Z score for height</th>
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<tr>
<td><strong>UK 1998-99 Surveillance</strong></td>
<td>Age &lt; 16 yrs (n=143)</td>
<td>-0.12 (95% CI -0.30 to +0.05)</td>
</tr>
<tr>
<td><strong>Toronto 2001-2009</strong></td>
<td>Tanner I/II (n=95)</td>
<td>+.11 (SD 1.0) +0.08 (IQR -0.5 to +0.7)</td>
</tr>
</tbody>
</table>

Sawczenko, Arch Dis Child 2003; Walters 2009
Height Z scores: patients with UC
(n=205 in PUCAI weighting and validation study)

Mean: -0.11
95%CI  -0.26, 0.05
SD: 1.12
Pathogenesis of growth impairment in Crohn disease: inter-related factors

- Direct growth-inhibiting effect of pro-inflammatory cytokines (TNF-α, IL-1, IL-6)
- Nutritional insufficiency: inadequate intake (anorexia), stool losses (protein), increased needs
- Corticosteroid inhibition of linear growth (IGF-1 axis)

Walters TD, Nature Prac Clin Gastroenterology 2009
“Restoration or maintenance of normal growth is a marker of therapeutic success”

- Increased needs
- Suboptimal intake
- MALNUTRITION
  - Inflammation
  - GROWTH IMPAIRMENT
    - Pubertal Delay
    - Corticosteroids

Inflammation
Pathogenesis of growth impairment in Crohn disease

- Role of disease-modifying genes
  - IL-6 polymorphisms?

Sawczenko A, PNAS 2005; 102: 13260
Basic principles in optimizing linear growth in IBD

- Identify pre-illness height centiles (and assess parental heights): assess deficits at diagnosis

- Regularly measure heights, assess height velocity (most sensitive parameter) in context of pubertal stage

- Provide optimal treatment for intestinal inflammation, guided by location, extent and nature
Ultimate stature in Crohn disease determined by:

- Genetically determined pre-illness height centile
- Duration of undiagnosed chronic inflammation (required catch-up growth)
- Adequacy of treatment in controlling inflammation following disease recognition
IBD Treatment goals

TRADITIONAL TREATMENT GOALS

- Induce and maintain clinical remission (symptom control)
- In children facilitate growth (a marker of success of therapy)

NEW TREATMENT GOAL

- Achieve and maintain mucosal healing
Is mucosal healing particularly important in children?

- Growth facilitation

- Prevention of disease complications over long life ahead
Steroids: Infrequent mucosal healing despite clinical remission

Clinical remission with steroids is not associated with mucosal healing

Endoscopic status in patients with clinical remission after 7 weeks of prednisolone 1 mg/kg daily (n=131; 92% of total population)

Specific interventions: Linear growth as outcome in paediatric clinical trials or observational studies

- Enteral nutrition
- Azathioprine
- Surgical resection
- Infliximab
- Methotrexate

Newby, Cochrane review 2005
Linear growth as outcome: requires longterm paediatric studies

<table>
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<tr>
<th>TREATMENT</th>
<th>CONTROLLED TRIALS</th>
<th>OBSERVATIONAL DATA</th>
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<tbody>
<tr>
<td>Enteral Nutrition</td>
<td>Yes: +ve</td>
<td>Yes: +ve</td>
</tr>
<tr>
<td>Surgery</td>
<td>No</td>
<td>Yes: +ve</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Yes: -ve</td>
<td>?</td>
</tr>
<tr>
<td>Methotrexate*</td>
<td>No</td>
<td>Yes: +ve</td>
</tr>
<tr>
<td>Infliximab</td>
<td>REACH study:+ve</td>
<td>Yes: +ve</td>
</tr>
</tbody>
</table>

* Turner, Am J Gastro 2007
Canadian Paediatric Crohn Disease Study: Cyclical enteral nutrition vs alternate day prednisone

**RCT duration: 18 months**

<table>
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<tr>
<th>Treatment</th>
<th>Number without relapse</th>
<th>Change in SDS for height</th>
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<tr>
<td>Vital HN N=18</td>
<td>12 (67%)</td>
<td>+0.40 (+/- 0.14)</td>
</tr>
<tr>
<td>Eod prednisone N=19</td>
<td>9 (47%)</td>
<td>-0.20 (+/-0.09)</td>
</tr>
</tbody>
</table>

Seidman, 1996
6-MP Maintains Remission in Paediatric Crohn Disease

Markowitz et al, *Gastroenterology*, 2000
Surgical resection of localized disease

Griffiths, Gut 1991

Small bowel  n=10
Terminal ileum +/- cecum  n=46
T.I. +/- Right colon  n=8
Ileocolonic  n=16

Cumulative proportions relapse-free

Time in years (follow-up)
Infliximab in paediatric CD
“chronically active despite prior immunomodulatory therapy”

Clinical Response at 10 weeks

Clinical Remission at 10 weeks

Induction = 5 mg/kg infusions at weeks 0, 2, 6

Infliximab in children with Crohn’s Disease: REACH Trial (n=112)

Responders at week 10 randomized to q8 vs q12 week maintenance

Hyams et al, Gastroenterology 2007
Height Velocity: cm/year

![Graph showing height velocity comparison between baseline and week 54 with and without baseline steroids.](image)

- **No Baseline Steroids** (N=35)
- **Baseline Steroids** (N=19)
Growth during infliximab therapy in patients with otherwise chronically active severe Crohn disease: Sickkids, Toronto experience

- **Mild sx only**
- **Moderate exacerbations**
- **Chronically Severe** (Despite immunomodulators and often enteral nutrition)
- **Chronically severe then resection**
Effect of infliximab therapy on Height (SDS)
Mean age at start of infliximab 13.4 yrs (+/- 0.6)

Disease duration 3.3 yrs (+/-0.47 yrs)

63% males

Follow-up 25mth (+/-8.7mth)

Walters T, Inflamm Bowel Dis 2007
Spectrum of pre-pubertal Crohn disease
(Global Symptom Severity: during 5 year follow-up from diagnosis)

1980 to 1989
n = 100

1990 to 1999
n = 163

Pre-pubertal Children from the Greater Toronto Area, SickKids, Toronto
Height at maturity: Crohn disease

- Onset of disease in pre- or early puberty
  - Height at diagnosis (n=161)
    - Mean z-score of -0.74
  - Height when followed to maturity (n=98)
    - Delta z-score
      - Overall: -0.03
      - Mild symptoms only: +0.28
      - Moderate exacerbations/remissions: -0.17
      - Chronically active: -0.25
      - Chronically active, then remission (surgery): +0.17

SickKids, Toronto 1990-1999
Anti-TNF therapy can potentially alter the spectrum and allow normal growth in a greater percentage of children.

- Mild sx only
- Moderate exacerbations
- Chronically Severe
- Chronically Severe, then resection

The current era
Optimal timing of anti-TNF therapy in paediatric CD

- When steroids or enteral nutrition fail?
- When immunomodulator fails to achieve steroid-free sustained remission?
- As initial active treatment in select patients....e.g. those with significant growth retardation at diagnosis?
- Importance of disease location and extent...e.g. severe colonic disease
Endoscopic healing was scored in 5 ileal and colonic segments as follows: 0=no ulcers, 1= aphthoid ulcers, 2=larger ulcers, 3= ulcerated stenosis.

† Endoscopic healing was scored in 5 ileal and colonic segments as follows: 0=no ulcers, 1= aphthoid ulcers, 2=larger ulcers, 3= ulcerated stenosis.

‡ p<.001

Our practice: timing of anti-TNF therapy in paediatric CD

- Steroid-refractory disease (usually colonic CD)

- For “steroid-responsive” patients, when immunemodulator fails to achieve steroid-free sustained remission...increasing use of MTX as first-line immunemodulator

- As initial active treatment in select patients
  - Severe perianal fistulizing disease
  - Consider for extensive, severe colonic disease
  - Delayed recognition of disease, growth impairment

- Consider disease location and extent
Our patient (diagnosed circa 2004)

- Initial treatment: corticosteroids – relatively refractory

- Infliximab induction and maintenance: now 5 years (initially in combination with azathioprine therapy, then monotherapy in 2006)

- ~9 mg/kg q 6 weeks (intermittent need to dose escalate/interval shorten)
Summary: Management or prevention of growth retardation

- Early recognition of IBD

- Systematic evaluation of linear growth

- While growth potential exists, optimize medical treatment to control inflammation; biologic therapy is an advance

- Surgical intervention for localized and complicated disease