NOVITA’ DIAGNOSTICHE E TERAPEUTICHE NELLE BASSE STATURE IDIOPATICHE

S. Bernasconi
S. Cesari, L. Melandri, M. Garrubba

Dipartimento dell’Età Evolutiva - Clinica Pediatrica - Università degli Studi di Parma
1985 - Biosynthetic GH approved by FDA for:

• GH deficiency
• Chronic renal insufficiency
• Turner syndrome
• Prader Willi syndrome
• Achondroplasia
• AIDS wasting adults
• GHD adults

2001 – SGA

2003 - Short “normal” children
Novità diagnostiche e terapeutiche nelle basse stature idiopatiche

Definizione:
1) Taglia normale alla nascita in rapporto all’età gestazionale
2) Normali proporzioni corporee
3) Assenza di deficit ormonali
4) Assenza di malattie croniche organiche o psichiatriche
5) Normale stato nutrizionale
6) Velocità di crescita basso-normale

Ranke MB  Horm Res 1996
Criteri per l’impiego del GH nel trattamento della ISS

1) No diagnosis of GH deficiency:
   -Exclusion of causes of growth failure that requires other therapeutic approaches
   -Exclusion of other causes of short stature, such as skeletal dysplasias, syndromic conditions and systemic disease

2) Height that is more than 2.25 DS below the mean for sex and age

3) Open epiphyses

4) Growth rate that is unlikely to attain an adult height within the normal range

(Recommendations of FDA, 2003)
Spontaneous Adult Height in Children with ISS
Novità diagnostiche e terapeutiche nelle basse stature idiopatiche

…in USA more than 410000 children could potentially receive Gh…
Novità diagnostiche e terapeutiche nelle basse stature idiopatiche
Editorial: Growth Hormone Treatment of "Idiopathic Short Stature": Not So Fast

Michael Freemark

Division of Pediatric Endocrinology and Diabetes Duke University Medical Center Durham, North Carolina 27710
“...To treat or not to treat: this is the question...”
To treat or not to treat: this is the question

PRO
To treat or not to treat: this is the question

PRO

1) Deficit staturale simile ad altre categorie
Patients with ISS Have Similar Severity of Short Stature to Other Disorders

**Patient Group**

- GHD*
- CRI*
- TS**
- SGA**
- ISS*

*Mean ± SD

*National Cooperative Growth Study
**Kabi International Growth Study
To treat or not to treat: this is the question

**PRO**

1) Deficit staturale simile ad altre categorie
2) Terapia efficace
Terapia con GH: PRO

• **Miglioramento della statura finale:**

  Finkelstein et al. 2002: Meta-analisi (10 studi)

  **Guadagno di 4-6 cm dopo 5,3 anni di trattamento**

In: The Cochrane Library, Issue 1, 2004

**Review:** Recombinant growth hormone for idiopathic short stature in children and adolescents

**Comparison:** 01 Growth hormone vs no treatment

**Outcome:** 03 Growth velocity Standard Deviation Score (1 year)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment N</th>
<th>Control N</th>
<th>Weighted Mean Difference (Random) 95% CI</th>
<th>Weight (%)</th>
<th>Weighted Mean Difference (Random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volta 1993</td>
<td>6</td>
<td>6</td>
<td>-3.50 [0.26, 6.71]</td>
<td>100.0</td>
<td>-3.50 [0.26, 6.71]</td>
</tr>
</tbody>
</table>

**Review:** Recombinant growth hormone for idiopathic short stature in children and adolescents

**Comparison:** 01 Growth hormone vs no treatment

**Outcome:** 02 Growth velocity (1 year)

<table>
<thead>
<tr>
<th>Study</th>
<th>Growth hormone N</th>
<th>Growth hormone Mean (SD)</th>
<th>No treatment N</th>
<th>No treatment Mean (SD)</th>
<th>Weighted Mean Difference (Random) 95% CI</th>
<th>Weight (%)</th>
<th>Weighted Mean Difference (Random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genentech 1989</td>
<td>50</td>
<td>7.30 (1.20)</td>
<td>44</td>
<td>4.70 (1.10)</td>
<td>2.60 [2.13, 3.07]</td>
<td>81.7</td>
<td>2.60 [2.13, 3.07]</td>
</tr>
<tr>
<td>Soliman 1996</td>
<td>12</td>
<td>7.80 (1.20)</td>
<td>12</td>
<td>5.50 (1.50)</td>
<td>2.10 [1.01, 3.19]</td>
<td>15.0</td>
<td>2.10 [1.01, 3.19]</td>
</tr>
<tr>
<td>Volta 1993</td>
<td>6</td>
<td>8.00 (2.40)</td>
<td>6</td>
<td>8.00 (1.47)</td>
<td>1.49 [-0.89, 3.89]</td>
<td>9</td>
<td>1.49 [-0.89, 3.89]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>68</td>
<td>8.00 (2.40)</td>
<td>62</td>
<td>8.00 (1.47)</td>
<td>2.48 [2.06, 2.90]</td>
<td>100.0</td>
<td>2.48 [2.06, 2.90]</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square = 1.18 df = 2 p = 0.4534
Test for overall effect = 11.59 p = 0.00001
Terapia con GH: PRO

• Miglioramento della statura finale:

  Leschek et al. 2004: guadagno 3,7 cm dopo 4,4 anni di trattamento a 0,22 mg/kg

Effetto dose-dipendente

  Witt et al. 2002: guadagno fino a 7 cm a 0,37 mg/kg → dosaggio max approvato
To treat or not to treat: this is the question.

**PRO**

1) Deficit staturale simile ad altre categorie
2) Terapia efficace
3) Sicuramente normale?
Evoluzione delle conoscenze

Nuove tecniche diagnostiche

Meno diagnosi di ISS

Circa il 25% dei bambini valutati per ISS presentano un deficit primario di IGF-1 in presenza di una normale secrezione di GH

Rosenfeld et al., J Clin Endocrinol Metab 2004
IGF-I in Patients with Idiopathic Short Stature

Baseline IGF-I SDS for all patients enrolled in placebo-controlled study

n=67
... it must be recognized that ISS represents a heterogeneous group of disorders, many such cases are likely to prove to have subtle defects of the multiple genes involved in the regulation of the skeletal response to endogenous GH...

Rosenfeld & Hwa, 2004
The Growth Axis

A Novel Dysfunctional Growth Hormone Variant (Ile179Met) Exhibits a Decreased Ability to Activate the Extracellular Signal-Regulated Kinase Pathway
M.D. Lewis et al J Clin Endocrinol Metab 2004

The tight interaction between the side chain of GH residue Ile179 and GHR residue Trp169. The Ile179 residue is depicted by a space-filling model. Trp169 is represented as a stick model, whilst the molecular surface of GHR residues 167–169 is shown in green.
Meccanismi molecolari responsabili di resistenza al GH

Altreazioni prerecettoriali:

- Dominio extracellulare del GHR
- Dimerizzazione del GHR
- Dominio transmembrana di GHR
- Dominio intracellulare del GHR
Meccanismi molecolari responsabili di resistenza al GH

**Alterazioni postrecettoriali:**

- JAK2
- STAT5b
- STAT5a
- ERK

- Regolazione trascrizionale di IGF-1
- Gene codificante IGF-1
- IGFBP
- IGF1-R
- Trasduzione del segnale di IGF1-R
- Alterata risposta ossea
Growth Hormone Insensitivity Associated with a STAT5b Mutation

## Defects of GHR Signaling Resulting from Mutations of the *STAT5b* Gene

### Table 1. Identified cases of homozygous *STAT5b* mutations

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>16.5</td>
<td>16</td>
<td>16</td>
<td>2.1</td>
<td>3.9</td>
<td>31</td>
</tr>
<tr>
<td><strong>Parental consanguinity</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
</tr>
<tr>
<td><strong>Paternal height (cm) (SD)</strong></td>
<td>173.6 (−0.3)</td>
<td>169 (−0.9)</td>
<td>160 (−2.2)</td>
<td>167.7 (−1.3)</td>
<td>167.7 (−1.3)</td>
<td>164.3 (−2.8)</td>
</tr>
<tr>
<td><strong>Maternal height (cm) (SD)</strong></td>
<td>155.8 (−1.2)</td>
<td>160 (−0.6)</td>
<td>142.3 (−3.3)</td>
<td>160.2 (−0.6)</td>
<td>160.2 (−0.6)</td>
<td>156.6 (−0.8)</td>
</tr>
<tr>
<td><strong>Place of origin</strong></td>
<td>Argentina</td>
<td>Turkey</td>
<td>Argentina</td>
<td>Kuwait</td>
<td>Kuwait</td>
<td>Caribbean</td>
</tr>
<tr>
<td><strong>Birth length (cm)</strong></td>
<td>NA</td>
<td>49</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>50</td>
</tr>
<tr>
<td><strong>Birth weight (g)</strong></td>
<td>1400</td>
<td>2350</td>
<td>2500</td>
<td>NA</td>
<td>NA</td>
<td>3270</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>117.8</td>
<td>114</td>
<td>102.7</td>
<td>69</td>
<td>79</td>
<td>141.8</td>
</tr>
<tr>
<td><strong>Height (SD)</strong></td>
<td>−7.5</td>
<td>−7.8</td>
<td>−9.9</td>
<td>−5.8</td>
<td>−5.6</td>
<td>−5.9</td>
</tr>
<tr>
<td><strong>IGF-I (basal) (ng/ml)</strong></td>
<td>38</td>
<td>7</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>14</td>
</tr>
<tr>
<td><strong>IGF-I (peak generated) (ng/ml)</strong></td>
<td>55</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>78</td>
</tr>
<tr>
<td><strong>IGFBP-3 (ng/ml)</strong></td>
<td>874</td>
<td>543</td>
<td>NA</td>
<td>700</td>
<td>800</td>
<td>180</td>
</tr>
<tr>
<td><strong>ALS (µg/ml)</strong></td>
<td>2.9</td>
<td>1.2</td>
<td>NA</td>
<td>0.4</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>GH (basal) (ng/ml)</strong></td>
<td>9.4</td>
<td>14.2</td>
<td>6.6</td>
<td>NA</td>
<td>NA</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>GH (stimulated) (ng/ml)</strong></td>
<td>53.8</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>14.2</td>
</tr>
<tr>
<td><strong>GHBp (pmol/l)</strong></td>
<td>1236</td>
<td>1232</td>
<td>NA</td>
<td>569</td>
<td>1311</td>
<td>1524</td>
</tr>
<tr>
<td><strong>GHR gene</strong></td>
<td>Wild-type</td>
<td>Wild-type</td>
<td>NA</td>
<td>Wild-type</td>
<td>Wild-type</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Prolactin (ng/ml)</strong></td>
<td>102–168</td>
<td>NA</td>
<td>169</td>
<td>NA</td>
<td>NA</td>
<td>110</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td>Pulmonary infections, lymphocytic interstitial pneumonia</td>
<td>Pulmonary infections, pulmonary fibrosis</td>
<td>Pulmonary infections, pulmonary fibrosis</td>
<td>Arthritis</td>
<td>Pulmonary infections</td>
<td>Hemorrhagic varicella</td>
</tr>
<tr>
<td><strong>Puberty</strong></td>
<td>Delayed</td>
<td>Delayed</td>
<td>NA</td>
<td>–</td>
<td>–</td>
<td>Delayed</td>
</tr>
<tr>
<td><strong>STAT5b gene</strong></td>
<td>A630P</td>
<td>1191insG</td>
<td>R152X</td>
<td>1680delG</td>
<td>1680delG</td>
<td>1103insC</td>
</tr>
<tr>
<td><strong>Refs</strong></td>
<td>[30]</td>
<td>[52]</td>
<td>[55]</td>
<td>[54]</td>
<td>[54]</td>
<td>[53]</td>
</tr>
</tbody>
</table>
## GH Insensitivity Syndromes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Phenotype</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GHR mutations/AR</strong></td>
<td>Laron syndrome</td>
<td>Laron, JCEM 2004, 89:1031-1044.</td>
</tr>
</tbody>
</table>
# GH Insensitivity Syndromes

<table>
<thead>
<tr>
<th>Molecular defect</th>
<th>Height</th>
<th>Birth size</th>
<th>GH</th>
<th>GHBP</th>
<th>IGF-1</th>
<th>IGFBP-3</th>
<th>ALS</th>
<th>Immune defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHR (extracellular domain)</td>
<td>↓↓</td>
<td>–</td>
<td>††</td>
<td>N-H</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>–</td>
</tr>
<tr>
<td>GHR (dimerization defect)</td>
<td>↓↓</td>
<td>–</td>
<td>††</td>
<td>N</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>–</td>
</tr>
<tr>
<td>GHR (transmembrane defect)</td>
<td>↓↓</td>
<td>–</td>
<td>††</td>
<td>N-†</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>–</td>
</tr>
<tr>
<td>GHR (intracellular domain)</td>
<td>↓↓</td>
<td>–</td>
<td>††</td>
<td>N-†</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>–</td>
</tr>
<tr>
<td>STAT5</td>
<td>↓↓</td>
<td>–</td>
<td>††</td>
<td>N</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>variable</td>
</tr>
<tr>
<td>ALS</td>
<td>↓</td>
<td>–</td>
<td>†</td>
<td>N</td>
<td>↓↓</td>
<td>↓↓</td>
<td>absent</td>
<td>–</td>
</tr>
<tr>
<td>IGF-I gene deletion</td>
<td>↓↓</td>
<td>↓↓</td>
<td>††</td>
<td>N</td>
<td>absence</td>
<td>↑</td>
<td>↑</td>
<td>–</td>
</tr>
<tr>
<td>IGF-I bioinactive</td>
<td>↓↓</td>
<td>↓↓</td>
<td>††</td>
<td>N</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>–</td>
</tr>
</tbody>
</table>
Conclusions:
Heterozygous mutations of the GHR gene are uncommon in Italian ISS patients, who are selected for adequate GH levels. However the observed incidence of 2 mutations out of 37 ISS patients (i.e., 5%) is not different from the one previously reported in the literature.
Other Potential Defects of GHR Signaling

c.172A>C (p.Asn58His)*
c.178G>T (p.Gly60Cys)*
c.179G>C (p.Gly60Ala) (n=2)
c.181G>A (p.Asp61Asn) (n=2)
c.182A>G (p.Asp61Gly)
c.184T>G (p.Tyr62Asp)
c.188A>G (p.Tyr63Cys)
c.214G>T (p.Ala72Ser)
c.844A>G (p.Ile282Val)
c.854T>C (p.Phe285Ser) (n=2)
c.922A>G (p.Asn308Asp) (n=6)
c.1502G>A (p.Arg501Lys)

PTPN11
12q24.1

SHP-2 NH2 N-SH2 C-SH2 PTP COOH
SOCS2 negatively regulates growth hormone action in vitro and in vivo

Christopher J. Greenhalgh,1 Elizabeth Rico-Bautista,2 Mattias Lorentzon,3 Anne L. Thaus,4 Phillip O. Morgan,1 Tracy A. Willson,1 Panagiota Zervoudakis,4 Donald Metcalf,1 Ian Street,1 Nicos A. Nicola,1 Andrew D. Nash,4 Louis J. Fabri,4 Gunnar Norstedt,2 Claes Ohlsson,3 Amilcar Flores-Morales,2 Warren S. Alexander,1 and Douglas J. Hilton1
Long-Term Treatment with Recombinant Insulin-Like Growth Factor (IGF)-I in Children with Severe IGF-I Deficiency due to Growth Hormone Insensitivity

Steven D. Chernausek, Philippe F. Backeljauw, James Frane, Joyce Kuntze, and Louis E. Underwood, for the GH Insensitivity Syndrome Collaborative Group*

Department of Pediatrics (S.D.C., P.F.B.), University of Cincinnati College of Medicine, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio 45229; Tercica, Inc. (J.K.), Brisbane, California 94005; Independent Consultant (J.F.), Santa Monica, California 90403; and Department of Pediatrics (L.E.U.), University of North Carolina, Chapel Hill, North Carolina 27599

HV media all’inizio della terapia 2.8 cm/anno
HV media dopo 1 anno 8 cm/anno
Altri geni coinvolti

Alterazioni gene codificante per il recettore B (NRP2) del peptide natriuretico C (CNP)

Alterazione di entrambi gli alleli

- Bassa statura
- Displasia scheletrica
- Sproporzione corporea (Displasia Acromesomelica)

Alterazione di un singolo allele

Possibile causa di ISS (senza displasia)

*Onley RC et al, JCEM, 2006*
C-type natriuretic peptide in growth: A new paradigm

Robert C. Olney *

Fig. 4. A model of CNP regulation of the growth plate (see text for details). The zones of the growth plate are labeled: R, reserve zone; P, proliferative zone; PH, prehypertrophic zone; and H, hypertrophic zone.
C-type natriuretic peptide in growth: A new paradigm

Robert C. Olney *

Growth Hormone & IGF Research 16 (2006) S6–S14

Fig. 5. Stature of carriers of the NPR2 1092delT mutation. The heights of carrier and noncarrier family members were measured and values transformed into z-scores. The points show the individual results (circles show the female subjects; squares show the male subjects). The mean for each group (±SD) is shown. The horizontal line shows the population mean (z-score of 0). *P < 0.0005 versus noncarrier family members. †P < 0.0005 versus general population. (Reprinted with permission from Olney et al. [64].)

Fig. 6. Other characteristics of carriers of the NPR2 1092delT mutation. The values for BMI, sitting height/height ratio (SH/Ht), head circumference (HC), heart rate, CNP, NT-proCNP, IGF-I, and IGFBP-3 of carrier and noncarrier family members were determined and transformed into z-scores. The open points show the mean of the carriers; the closed points show the mean of the noncarriers (values are mean ± SD). For the carriers, n = 14 for BMI, HC, and heart rate, and n = 8 for the other measures. For the noncarriers, n = 23 for BMI, HC, and heart rate, and n = 15 for the other measures. *P < 0.05 versus noncarrier family members. †P < 0.05 versus the general population. (Reprinted with permission from Olney et al. [64].)
Altri geni coinvolti

Alterazioni gene codificante per il recettore della vitamina D (FOK1)

ISS

* Dempfle A et al, Hum Molec Gen, 2006
Fig. 1. The complex regulation of linear growth involves several pathways, including the GH-IGF-1 axis, direct effects of GH on bone metabolism, SHOX gene alteration of bone growth, and many others. In children who otherwise might be considered to have ISS, genetic defects have been found at multiple steps of the GH-IGF-1 pathway (labeled 1 to 5) as well as in the SHOX gene (6) (see Table 1). In IGF-1 generating cells, GH (1) binds to the GHR (2), leading to receptor dimerization and functional receptors at the cell surface membrane. These active receptors then stimulate the associated JAK2, which undergoes autophosphorylation and phosphorylates the GHR. The GHR-JAK2 complex activates other signaling pathways including STAT (3) and ERK. STAT translocation to the nucleus induces transcription of the IGF-1 gene, which results in the generation of circulating IGF-1 (4). IGF-1 interacts with IGF-1 receptors (5), leading to linear growth. ERK activation leads to nuclear translocation and immediate early gene transcription, but is not linked to IGF-1 gene transcription. The SHOX gene (6) is present in bone marrow fibroblasts; its functional effect is not known. Other factors involved in the regulation of growth are not specified in this figure, which focuses only on currently identified sites of defects.
SHOX is located within PAR1.
SCHEMATIC DIAGRAM OF THE GENOMIC STRUCTURE OF SHOX GENE
Leri and Weill

Une affection congénital et symétrique du développement osseux: la dyschondrostéose

Mesomelic Short Stature

- high-arched palate, micrognathia
- cubitus valgus
- Madelung deformity
- short 4th metacarpals
- genu valgum
- SHOX
Figure 2: Lateral and Dorsal Bowing of a Shortened Radius in Madelung Deformity
Figure 3: Features of Madelung Wrist Deformity
Families studied 21

Deletion 10

No deletion 11

Mutations

Familial cases 2

Normal 9

S. Bernasconi et al J Med Genet 2002
Schematic diagram of the genomic structure of SHOX gene and position of point mutations identified


EX 1  EX 2  EX 3  EX 4  EX 5  EX 6A  EX 6B

75 VAL → STOP (del272G)

132 LEU → VAL (C485G)
136 PHE → LEU (T497C)
153 ARG → LEU (C549T)
125 THR → frame shift (del465C)

199 TYR → STOP (C688G)
195 ARG → STOP (C674T)
SHOX Gene Organization, Mutations and Related Disorders

*Rappold G et al, JCEM 87:1402, 2002*
Leri and Weill
To treat or not to treat: this is the question.

**PRO**
1) Deficit staturale simile ad altre categorie
2) Terapia efficace
3) Sicuramente normale?
4) Problemi psicologici?
Terapia con GH: PRO

- Fattori psicosociali:

  *Bassa statura = disturbi del comportamento?*
  *Problemi emotivi?*
  *Ridotta autostima?*
To treat or not to treat: this is the question.
Treat or not to treat: this is the question.

CONTRO
1) Effetti indesiderati?
Terapia con GH: CONTRO

- Assenza di studi a lungo termine sull’impiego del GH
- Assenza di un effettivo vantaggio funzionale determinato da un incremento staturale di 4-7 cm
- Rischio di frustrazione per il mancato raggiungimento di una statura soddisfacente nonostante la terapia
Safety of GH therapy

IGF-I levels should be monitored during GH treatment. If repeated measurements of IGF-I exceed + 2 SD scores compared to age- and pubertal-matched reference values, the IGF-I:IGFBP-3 ratio should be used as a guide for dose adjustment.
To treat or not to treat: this is the question.

CONTRO
1) Effetti indesiderati?
2) Efficace?
Effect of Growth Hormone Treatment on Adult Height in Peripubertal Children with Idiopathic Short Stature: A Randomized, Double-Blind, Placebo-Controlled Trial

E.W.Leschek et al
J Clin Endocrinol Metab 89, 3140-3148
2004
... while many of the studies found that children with short stature were at greater risk to have test scores lower than their peers, most short children still had IQs, academic achievement, and behavior within normal range. The reason for this discrepancy is not clear.

... no study found a direct casual link between short stature and functional impairment.
Short Stature and functional impairment: A systematic Review

P.G. Wheeler et al
Arch Pediatr Adolesc Med 2004

...currently, there is no evidence that deficits in intelligence, academic achievement, or behavior would improve if short children gained additional height....
To treat or not to treat : this is the question.

CONTRO
1) Effetti indesiderati?
2) Efficace?
3) Heightism
Le scelte terapeutiche problematiche: la terapia con l’ormone della crescita negli “short normal”

…there is a risk of increasing the “heightism”…

L. Cuttler Arch Ped Adol Med 2004
Cina, corsa a diventare più alti
dal chirurgo per avere successo

almeno il 30 per cento dei pazienti, ma diventa a quanto uno che mi
naccia di togliere la vita cosa pos-
sa fare?-
Alla quale, appunto. Xia Hetao
ha cliniche in tutto il paese. L'una
terzo e nata quando ha eseguito
una nipote del presidente Deng
Xiao Ping.
Non è il solo a vendere centi-
metri. Ce ne sono molti altri. In
Cina la sanità è privata. Da Cen-
tong una ragazza di 24 anni chiede
le sue solferuzioni al telefono.
"Non riesco ad alzarmi dal letto.
Volevo ammazzarmi dal dolore.
Ma ho tentato al contatto con i
medici, i medici con la mia per
chiodo nelle gambe, per cinque
mesi dallo strazio ho dormito solo

La Repubblica
20 Luglio 2004
Is height related to longevity?
Samaras TT, Elrick H, Storms LH.

Life Sci. 2003 Mar 7;72(16):1781-802
Is height related to longevity?
Samaras TT, Elrick H, Storms LH.

Life Sci. 2003 Mar 7;72(16):1781-802
To treat or not to treat: this is the question.

CONTRO
1) Effetti indesiderati?
2) Efficace?
3) Heightism
4) Costi economici
Le scelte terapeutiche problematiche: la terapia con l’ormone della crescita negli “short normal”

Il costo stimato è di 35.000 dollari ogni 2,5 cm guadagnati

Finkelstein 2002
Le scelte terapeutiche problematiche: la terapia con l’ormone della crescita negli “short normal”

…it is quite possible that the looming costs will cause some insurers to exclude Gh treatment as a benefit for their entire insured populations…

L. Cuttler Arch Ped Adol Med 2004
To treat or not to treat: this is the question.
Conclusioni

Necessità di miglioramento degli strumenti diagnostici, prognostici e di follow-up

Necessità di fornire informazioni corrette ed approfondite alla famiglia

Necessità di criteri di selezione precisi per una migliore risposta alla terapia

Ridotta velocità di crescita pre-terapia
Ritardo di maturazione ossea
Ridotti livelli di IGF-1
Ridotte dimensioni dell’ipofisi RMN
Maggiore velocità di crescita nei primi 6-12 mesi di terapia

Freemark M, JCEM 2004)
A common polymorphism of the growth hormone receptor is associated with increased responsiveness to growth hormone.

Chiara Dei Spera1, Lorenza Bonanno1, Carlotta Barletta1, Matteo Salvia1, Vincent Goffin1, A. Parisi Monastere2

Growth hormone is used to increase height in short children who are not deficient in growth hormone, but for whom there are genetic reasons why they are short. The genetic factors responsible for this condition are not clear. The authors describe a novel polymorphism in the growth hormone receptor gene that leads to increased responsiveness to growth hormone. They used a novel assay to detect the polymorphism, which they found was present in two of their patients. The assay was able to detect the polymorphism in blood samples from both patients, but not in blood samples from any of the controls. The authors propose that this polymorphism may explain some of the variability in response to growth hormone treatment. They suggest that further studies are needed to confirm these findings and to better understand the implications of this novel polymorphism.
Grazie per l’attenzione