

Evaluation of the response to Growth Hormone treatment in paediatric patients with diagnosis of Growth Hormone deficiency: an Empirical Bayes approach

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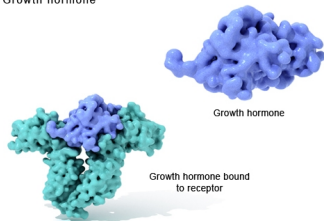
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Growth Hormone Deficiency

Growth hormone



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Growth Hormone Deficiency (GHD) is a pathological condition in which the body does not produce enough growth hormone (GH), (*Rosenfeld RG, 1996*)

Quigley CA, 2007

GH replacement therapy has been offered to children with GHD for more than 30 years. While the treatment was initially limited to children with severe forms of GHD, in 1985 the introduction of recombinant human GH increased the drug availability and permitted to treat a greater number of subjects, also with less severe forms of growth retardation.

Epidemiology

Incidence

- 1 in 30,000 Parkin et al. 1974:
- 2.8 in 100,000 (males), 1.7 in 100,000 (females), Stockholm et al. 2006

Prevalence

- Kabi International Growth Study
- Belgium (Thomas et al, 2004); Spain (Regal M et al., 2001); Coste et al., 1997(France)
- 9.44 in 100,000 (Migliaretti et al. 2006)

Few studies have demonstrated an increase in adult height at the end of rhGH treatment both in patients with idiopathic short stature and in patients with pituitary GH deficiency.

Approaches to GH replacement therapy assessment

Indirect approach: factors influencing the final growth at puberty in GHD patients are evaluated and subsequently used to estimate the overall effect at the end of growth

Ranke et al. 2003, Vosahlo et al. 2004

factors influencing the absolute growth and the height velocity (sex, age at onset, pubertal status, mean GH dose) are analyzed using multivariate linear regression models.

- *strength*: they allow for the calculation of the expected growth in a given individual from the starting time of GH therapy until adulthood height is reached.
- *weakness*: they consider the observed data as a multivariate measurement rather than curves of growth measured on each sampling unit.

Functional approach

N.S. Altman and G. Casella, 1995

For each individual, the height is a curve

$$\mu_i(t) = \mu(t) + \eta_i(t)$$

$\mu(t)$ is the mean curve over the whole population; $\eta_i(t)$ is the deviation of the individual curve from the mean curve at time t .

N individuals observed at times t_1, \dots, t_T

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$$y_{ij} = \mu_i(t_j) + \epsilon_{ij}$$

$\mu_i(t) \in C^1$; errors ϵ_{ij} have mean 0 and constant variance σ^2 .

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Linear smoothers

The estimate $\mu_i(t)$ is given by:

$$\hat{\mu}_i(t) = \sum_{j=1}^T w_{\lambda}(t, j) y_{ij}$$

Properties

- $E[\hat{\mu}_i(t) | \mu_i(\cdot)] = \sum_{j=1}^T w_{\lambda}(t, j) \mu_i(t_j) \neq \mu_i(t)$
- $[\hat{\mu}_i(t) | \mu_i(\cdot)] < [y_{ij} | \mu_i(\cdot)]$
- if the data are normally distributed
 $\Rightarrow (y_{11}, \dots, y_{NT}, \hat{\mu}_1(t_1), \dots, \hat{\mu}_N(t_T))$ is jointly Normal

Univariate Empirical Bayes Estimator

$$\hat{\mu}_i = \hat{\mu}_i(z_{i1}, \dots, z_{iT}) \quad z_{ij} \text{ iid for each fixed } i$$

$$\hat{\mu}_i = \psi_i + \nu_i \quad E(\psi_i) = \psi_i, \quad E(\nu_i) = 0, \quad \text{Var}(\nu_i) = \tau^2/T$$

Properties

$$\bar{\mu}_i = \frac{1}{N} \sum_{i=1}^N \mu_i \quad \bar{\hat{\mu}} = \frac{1}{N} \sum_{i=1}^N \hat{\mu}_i \Rightarrow \exists \alpha : \tilde{\mu}_i = \bar{\mu}_i + \alpha(\mu_i - \bar{\hat{\mu}})$$

$$\alpha = S_{\hat{\mu}\mu} / S_{\hat{\mu}\hat{\mu}} \quad \text{Since } S_{\hat{\mu}\hat{\mu}} > 0 \Rightarrow \alpha \text{ is negative only if } S_{\hat{\mu}\mu} < 0$$

EB as Hierarchical model

Hierarchical model

$$\begin{pmatrix} \hat{\mu}_i \\ \mu_i \end{pmatrix} \sim \text{Normal} \left(\begin{pmatrix} \psi \\ \mu \end{pmatrix}; \begin{pmatrix} \sigma_{\hat{\mu}}^2 & \sigma_{\psi\mu} \\ \sigma_{\psi\mu} & \sigma_{\mu}^2 \end{pmatrix} \right)$$

where $\sigma_{\hat{\mu}}^2 = \sigma_{\psi}^2 + \tau^2/T$

and the posterior mean of μ_i as Bayes estimator is:

$$\tilde{\mu}_i = \mu + B(\hat{\mu}_i - \psi), \quad B = \sigma_{\psi\mu} / \sigma_{\hat{\mu}}^2$$

Linear smoothing and EB estimation

When data are normally distributed, so is $\hat{\mu}(t)$ for a fixed smoothing parameter. Thus under the assumption that $\psi_i(t) = E[\hat{\mu}_i(t)|\mu(\cdot)]$ and $\mu_i(t)$ are normally distributed:

Hierarchical model

$$\begin{pmatrix} \hat{\mu}_i(t) \\ \mu_i(t) \end{pmatrix} \sim \text{Normal} \left(\begin{pmatrix} \psi(t) \\ \mu(t) \end{pmatrix}; \begin{pmatrix} \sigma_{\hat{\mu}(t)}^2 & \sigma_{\psi(t)\mu(t)} \\ \sigma_{\psi(t)\mu(t)} & \sigma_{\mu(t)}^2 \end{pmatrix} \right)$$

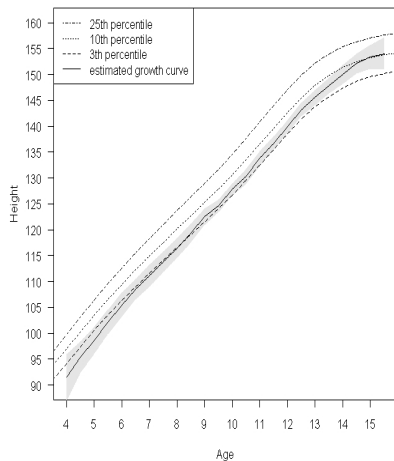
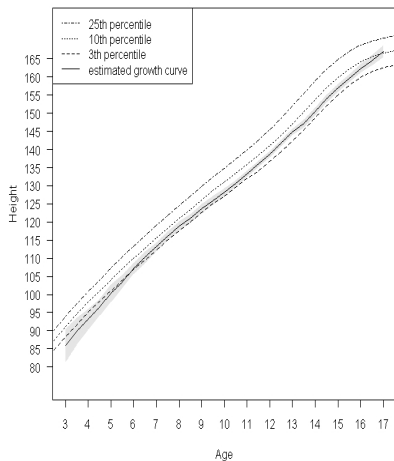
Patients included

- Pre-pubertal patients with pituitary GH deficiency [peak GH response < 10 or < 20 mcg/L (if the test was the GHRH + arginine tests) after 2 different provocative test] enrolled in the GH Registry during the period January 2000 - October 2008
- The Registry provided 402 patients suitable for this analysis (269 males and 133 females).

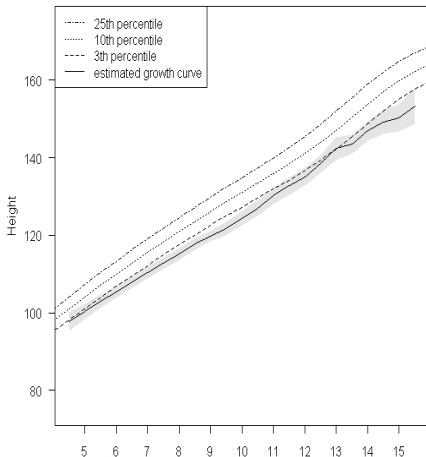
Descriptive statistics

	Females	Males	Overall
	N=133	N=269	N=402
Age at start	9.21(2.73)	10.23(3.37)	9.89(3.2)
Height at start	119.16(16.68)	125.15(18.25)	123.17(17.65)
SDS Height at start	-2.08(0.83)	-2.02(0.82)	-2.04(0.84)
Bone age at start	7.68(3.43)	8.27(3.84)	8.08(3.72)
Height-last visit	143.25(13.64)	151.42(17.74)	148.77(16.94)
SDS Height-last visit	-1.27(0.89)	-1.02(0.89)	-1.1(0.89)
Bone age - last visit	11.15(2.97)	12.7(3.65)	12.2(3.5)
Genetic potential	156.57(5.59)	168.86(5.93)	164.66(8.23)
Years of therapy	3.47(1.64)	3.7(1.98)	3.63(1.88)

Growth Curves



Pre-therapy growth curves



- Non-parametric and semi-parametric techniques have been often suggested as alternatives to parametric models for growth curve estimation. EB estimator provides a means of combining evidence across similar population
- EB methodology can improve the estimation of growth parameters in polynomial growth curve modeling
- slightly differences in onset ages could introduce greater variability in the estimated curves, particularly evident for extreme age ranges.

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