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Growth outcomes and near-adult height of children with congenital GH deficiency (GHD) due to abnormal pituitary development: Data from a prospective, multinational, observational study

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Potential conflict of interest may exist; please refer to abstract

BACKGROUND AND AIMS:

- Children with structural hypothalamic-pituitary anomalies usually have more severe GHD (1, 2) and better auxological outcomes with GH therapy compared to those with normal hypothalamic-pituitary magnetic resonance imaging (MRI) findings.
- However, data on adult height outcomes are limited.
- Using data from the prospective, observational Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS) we aimed to characterise short-term growth and near-adult height (NAH) outcomes in GH-treated patients with:
  - ectopic posterior pituitary (EPP) with/without pituitary stalk interruption syndrome
  - septo-optic dysplasia (SOD)
  - isolated anterior pituitary aplasia/hypoplasia (AP/HP), and
  - GH deficient patients with no reported hypothalamic-pituitary MRI findings (Other-GHD).

CONCLUSIONS:

- **Patients with structural hypothalamic-pituitary abnormalities had more severe GHD and greater height deficit than those without such abnormalities.**
  - **Structural pituitary anomalies are considered predictive of GHD (2).**
- **They appeared to have better outcomes of GH treatment, with EPP having the best first-year and NAH gain**
  - **but age at GH start and treatment duration varied.**
- **Limitations: Interpretation of significance is limited by difference in sizes of diagnostic groups.**

KEY RESULTS: Baseline

- Patients with EPP were:
  - younger than those with AP/HP or Other-GHD, but older than those with SOD (Table 1)
  - had shorter stature than those with SOD or Other-GHD.

Table 1: Baseline characteristics by diagnostic group [Mean (95% CI) for continuous variables]

	EPP	SOD	AP/HP	Other-GHD
N[1]	185	76	291	6095
Proportion with MPHD	52%	75%	30%	8%
Baseline age (y)	6.2 (5.6, 6.9)	4.5 (3.6, 5.4)*	8.9 (8.4, 9.5)*	10.2 (10.1, 10.3)*
Ht SDS	-3.0 (-3.2, -2.8)	-2.4 (-2.7, -2.1)*	-2.8 (-3.0, -2.7)	-2.4 (-2.4, -2.4)*
Ht SDS – THt SDS	-3.0 (-3.2, -2.8)	-2.7 (-3.1, -2.4)	-2.4 (-2.6, -2.3)*	-1.9 (-1.9, -1.8)*
BMI SDS	-0.8 (-1.1, -0.5)	-0.7 (-1.1, -0.2)	-0.9 (-1.1, -0.7)	-0.4 (-0.5, -0.4)*
Pretreatment HVSDS	-1.7 (-2.1, -1.3)	-2.0 (-2.8, -1.2)	-1.2 (-1.4, -1.0)	-1.0 (-1.1, -0.9)*
Maximum GH peak (ng/mL)	3.9 (3.1, 4.8)	2.9 (2.3, 3.5)	5.0 (4.6, 5.5)	8.2 (8.0, 8.4)*

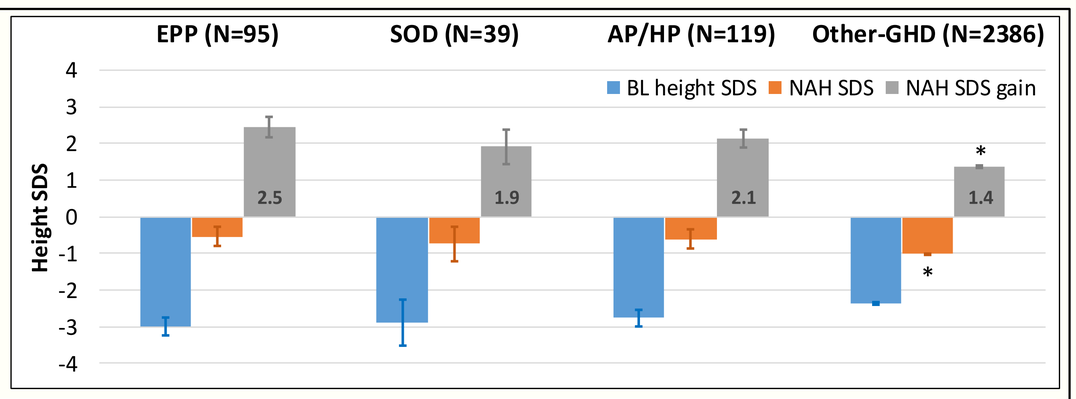
*Significantly different from EPP (non-overlap of 95% confidence limits)

[1]Maximum N (lower for some variables)

Abbreviations: BMI = body mass index, Ht = height, HV = height velocity, MPHD = multiple pituitary hormone deficiencies, N = number, SDS = standard deviation score, THt = target height (mid parental height), y = years

KEY RESULTS: Near-adult height

- Patients with EPP had:
  - the greatest height gain; significantly greater vs Other-GHD (Figure 2), albeit with earlier start/longer duration of GH treatment
  - later start/shorter GH therapy duration, but a better height outcome, than SOD (not significant).



	EPP (N=95)	SOD (N=39)	AP/HP (N=119)	Other-GHD (N=2386)
Age at NAH (y):	17.8 (17.4, 18.2)	17.3 (16.7, 17.8)	18.1 (17.7, 18.6)	17.2 (17.1, 17.3)*
Last GH dose[1]:	0.19 (0.17, 0.21)	0.21 (0.17, 0.26)	0.21 (0.20, 0.23)	0.27 (0.26, 0.27)*
Duration of GH (y):	9.2 (8.3, 10.0)	11.2 (9.7, 12.6)	7.9 (7.0, 8.9)	5.6 (5.5, 5.7)*

*Significantly different from EPP (non-overlap of 95% confidence limits); [1]mg/kg/week

Abbreviations: BL = baseline, CI = confidence interval, N = number, NAH = near-adult height, SDS = standard deviation score, y = years

Figure 2: Near-adult height outcomes (mean and 95% CI) for patients with GHD associated with hypothalamo-pituitary anomalies and those without such structural defects

METHODS:

Study

- GeNeSIS was a prospective, multinational, observational study collecting data on GH-treated paediatric patients with a broad variety of growth disorders from 1999 to 2015.
  - All decisions regarding GH treatment, including whether to treat and dose, were at the discretion of the investigators.

Patients

- Patients were grouped by investigator-provided diagnoses:
  1. EPP (including interrupted pituitary stalk [Figure 1]; irrespective of any other abnormal pituitary-associated finding, except SOD)
  2. SOD (irrespective of any other abnormal pituitary associated finding)
  3. AP/HP (no other abnormal pituitary-associated finding [Figure 1]), and
  4. Other-GHD (not acquired GHD/no pituitary abnormality).

Statistics

- Statistical significance between diagnostic groups was assessed by non-overlap of 95% confidence limits (CI); primary comparison was EPP vs other diagnostic groups.
- Height standard deviation score (SDS) was calculated using US age/sex-adjusted data (3).
- Adult height (NAH) was considered as achievement of at least one of the following: closed epiphyses, height velocity <2 cm/year, bone age >14 years (girls) / >16 years (boys).

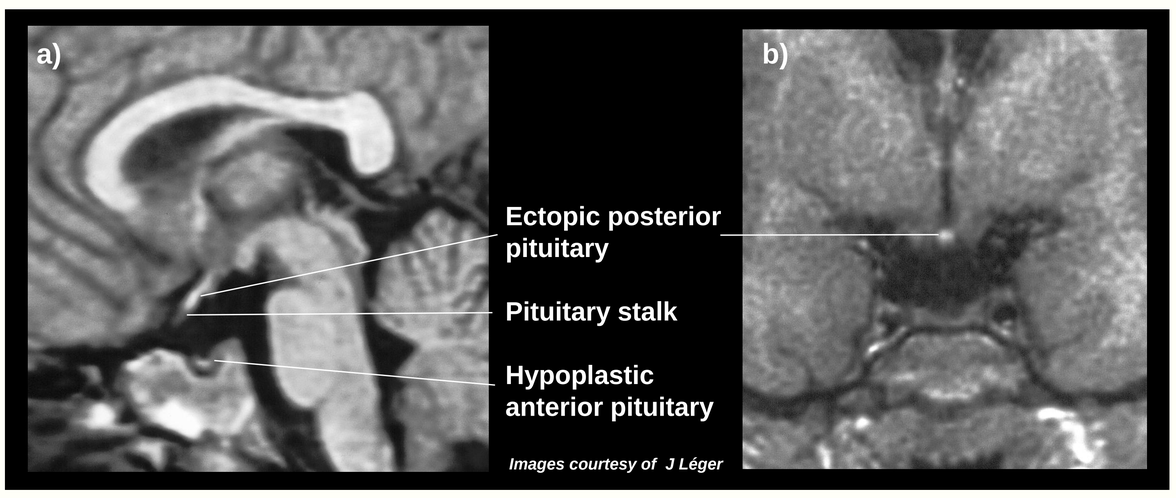
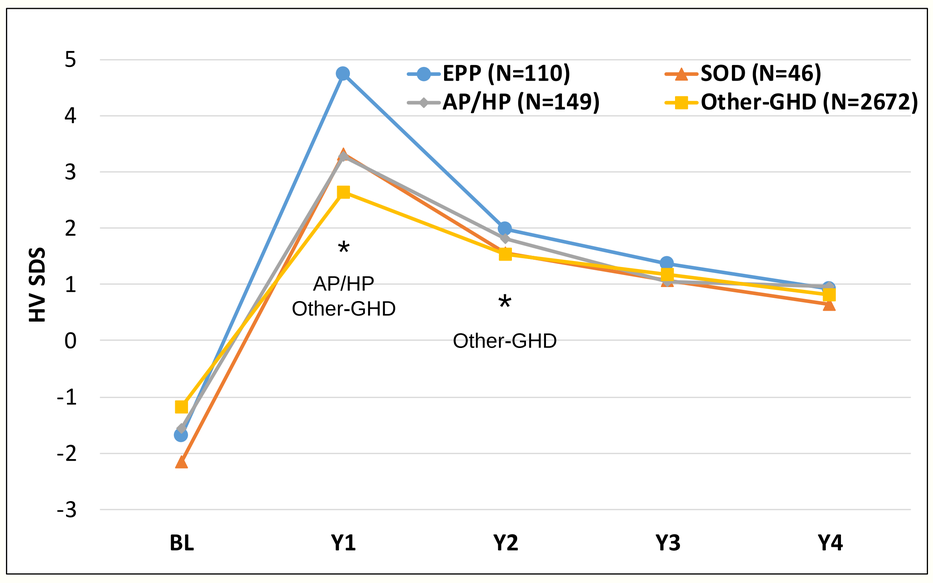


Figure 1: Mid-sagittal (a) and coronal (b) magnetic resonance images of pituitary stalk interruption syndrome in a 6-month old girl, with ectopic posterior pituitary, hypoplastic pituitary stalk and small flattened anterior pituitary within the pituitary fossa.

RESULTS: Short-term (1, 2, 3, and 4 year) height gains

- 1st-year height velocity SDS (Figure 3) and 1st-year Δheight SDS were greatest for EPP (significantly so versus AP/HP and Other-GHD):
  - 1st-year Δheight SDS [mean (95% CI) were 1.3 (1.1, 1.4) for EPP, 1.1 (0.9, 1.3) for SOD, 0.9 (0.8, 1.0) for AP/HP, and 0.6 (0.6, 0.6) for Other-GHD.
- As expected height velocity SDS was greatest in the 1st-year and diminished in subsequent years, but remained above zero for the 4-year observation period for all diagnoses (Figure 3).



*Significantly different from EPP (non-overlap of 95% confidence limits)

Abbreviations: BL = baseline, HV = height velocity, N = Number, SDS = standard deviation score, Y = year

Figure 3: Height velocity SDS during the first 4 years of GH treatment by diagnostic group

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