Etiology, Clinical Course and Predictors of Delayed Puberty in 244 Patients Evaluated in a Single Large Academic Center

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Introduction

The conditions that underlie delayed puberty (DP) can be categorized into constitutional delay of growth and puberty (CDGP), permanent hypogonadotropic hypogonadism (PHH), functional hypogonadotropic hypogonadism (FHH) and hypergonadotropic hypogonadism (Hyper H) (1). We investigated the etiology of DP and its outcome predictors in a tertiary center setting.

Design and participants

This retrospective chart review included clinical and biochemical data of 244 patients who were evaluated for DP at the Helsinki University Central Hospital between 2004 and 2014. The eligibility criteria are detailed in Figure 1.

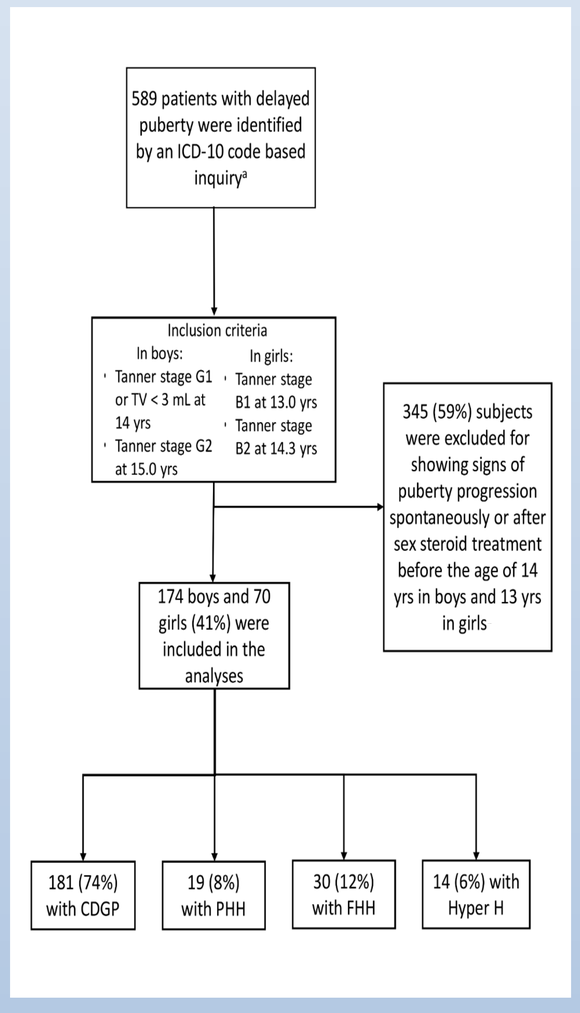

Figure 1. Enrollment and outcomes. [a]ICD-10 codes: E28, E28.3, E28.8, E28.9, E29, E29.0, E29.1, E29.8, E29.9, E30.00, E30.09, E30.8, and E30.9

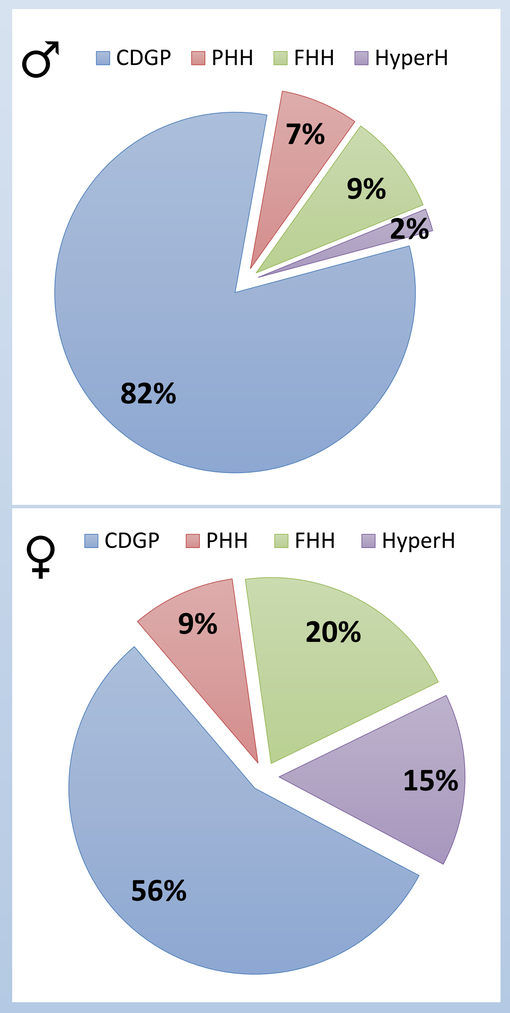

Figure 2. The distribution of etiologies underlying delayed puberty in the study subjects.

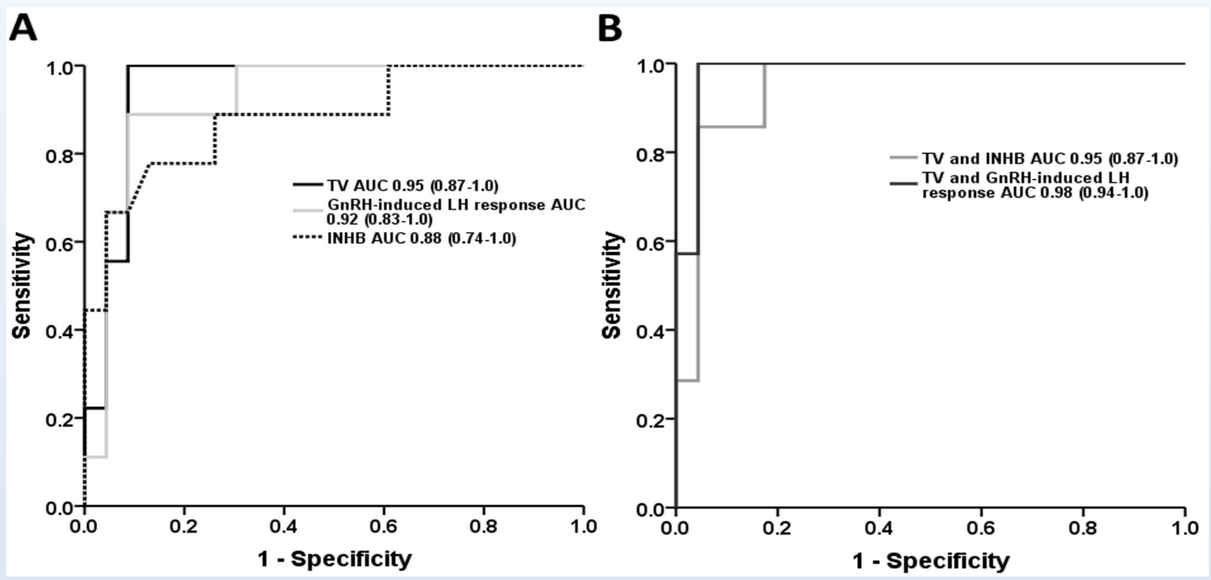

Figure 3. A, ROCs and AUCs with 95% confidence intervals for testis volume (TV), GnRH-induced LH and inhibin B (INHB) in 56 prepubertal boys with constitutional delay of growth and puberty (CDGP) and in 10 boys with congenital hypogonadotropic hypogonadism (CHH). B, ROCs for the combination of TV and INHB and TV and GnRH-induced LH.

- In the differentiation between the prepubertal boys with congenital hypogonadotropic hypogonadism (CHH) (n=10) and those with CDGP (n=56), the mean testicular volume (TV), with a cut-off level of 1.1 mL, appeared as the single most effective discriminatory marker (sensitivity 100%, specificity 91%) (**Figure 3A**).
- After we combined inhibin B or GnRH-induced LH levels with TV, a slightly more accurate level of discrimination was reached (**Figure 3B**).
- The combination of TV and inhibin B was subjected to a logistic regression analyses which produced a prediction model for the probability of CHH (**Table 1**).

Inhibin B (ng/L)	Testicular volume 0.1 – 1 mL	1.1 – 2 mL
10 - 49	90% (50-100%)	20% (0 – 80%)
49 - 111	60% (10-100%)	10% (0 – 40%)
111 – 212	20% (0-90%)	0% (0 – 10%)

Table 1. The mean disease risk predictions for congenital hypogonadotropic hypogonadism (CHH) depending on mean testicular volume and inhibin B levels in patients with delayed puberty and Tanner genital stage 1. Mean (range).

Results

- CDGP was the single most common cause for DP in both sexes, and it was more frequent in the boys than in the girls ($P < 0.001$) (**Figure 2**).
- FHH and Hyper H affected the girls more frequently than the boys ($P < 0.05$) (**Figure 2**).
- The conditions that cause FHH were more frequent in the boys with the growth velocity less than 3 cm/yr than in those growing faster (19% *vs* 4%, $P < 0.05$).
- A history of cryptorchidism in the boys was associated with an 8-fold increase in the risk of permanent hypogonadism (positive predictive value 57%, 95% CI; 20-88).

Conclusions

- In both sexes, CDGP is the most common cause of delayed puberty.
- A history of cryptorchidism and slow growth velocity are two important clinical cues that help to predict the clinical course of DP in boys.
- In prepubertal boys, testicular size is a simple diagnostic parameter of clinical value for differentiating between CDGP and CHH.

References

1. Sedlmeyer IL *et al.* JCEM 2002; 87:1613-20.

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