Precocious puberty: a single academic center experience

Heta Huttunen[1], Tero Varimo[2], Annika Tarkkanen[1], Johanna Hietamäki[1], Päivi J. Miettinen[2,3], Matti Hero[2,*] and Taneli Raivio[1,2,*]

[1]Faculty of Medicine/Physiology, University of Helsinki, Helsinki, Finland
[2]Children's Hospital, Helsinki University Central Hospital (HUCH), Helsinki, Finland
[3]BSCC & Research Programs Unit, Molecular Neurology, University of Helsinki, Finland
*Equal contribution

Introduction

Delayed and precocious puberty both represent rich veins for the identification of genes that regulate the timing of sexual maturation in humans. The purpose of this work is to identify novel genes that regulate puberty by taking advantage of the special genetic features of the Finns and the Finnish health care registries. Herein, we describe the diagnoses underlying PP in a single academic center with special attention in the identification of familial cases.

Patients and methods

We performed an ICD-10 code-based inquiry to the electronic patient records of the Children's Hospital, Helsinki University Central Hospital, in order to identify patients evaluated for precocious puberty between 2001 and 2014. The following ICD-10 codes were used: E22.80, E28, E28.8, E28.9, E29, E29.0, E29.8, E29.9, E30, E30.1, E30.8, E30.9, and Q78.1 (**Figure 1**). The girls and boys presenting with clinical signs of puberty before age 8 and 9 years, respectively (1), and girls with menarche at age 9.3 years or younger [representing the mean -3SD of healthy Finnish girls (2)], were included and classified into diagnostic subgroups (**Table 1**).

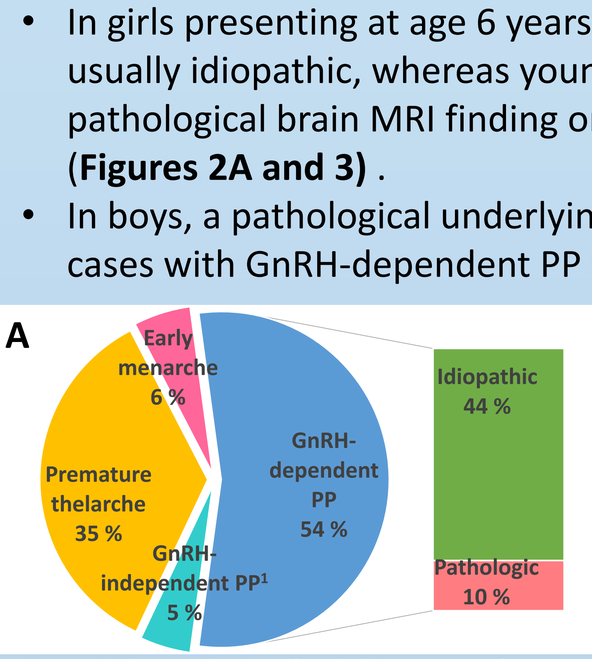

Figure 1. Identification and verification process of the patients with precocious puberty.

Table 1. Classification of patients presenting with signs of precocious puberty (3).

	Criteria in girls	Criteria in boys younger than 9 years
Premature thelarche (PT) in girls, and "Other" in boys	B2-5 less than 8 years of age and prepubertal LH*	G2, prepubertal LH* and testosterone <0.7 nM
GnRH-independent precocious puberty (PPP)	B2-5 less than 8 years of age, elevated estradiol and prepubertal LH	Androgen excess and prepubertal LH
GnRH-dependent precocious puberty# (CPP)	B2-5 less than 8 years of age and pubertal LH**	G2-5 and pubertal LH
Early menarche	menarche younger than 9.3 years (mean -3SD of healthy girls [2]).	NA

*Peak serum LH <5 IU/L in a GnRH stimulation test (4); **Peak serum LH >5 IU/L in a GnRH stimulation test, or basal serum LH ≥0.3 IU/L (4)
#, includes idiopathic central precocious puberty, adoption, acquired CNS insults and lesions, hypothalamic hamartoma, and neurofibromatosis type 1.

Results

- Girls (n=164) presented with PP ~10 times more frequently than boys (n=17).
- In both sexes, PP was most frequently GnRH-dependent.
- In girls presenting at age 6 years or older, GnRH-dependent PP was usually idiopathic, whereas younger girls predominantly had a pathological brain MRI finding or a disease that predisposes to PP (**Figures 2A and 3)** .
- In boys, a pathological underlying cause was identified in 47% of cases with GnRH-dependent PP (**Figure 2B**).

Figure 2. The distribution of underlying causes of premature puberty in 164 girls (panel A) and in 17 boys (panel B).
[1] MAS (n=7), ovarian cyst (n=1)
[2]Exposure to testosterone gel (n=2), Leydig cell tumor (n=1).

- Among patients with idiopathic GnRH-dependent precocious puberty (n=75), 22 (29%) had a history of precocious puberty in a first degree relative.

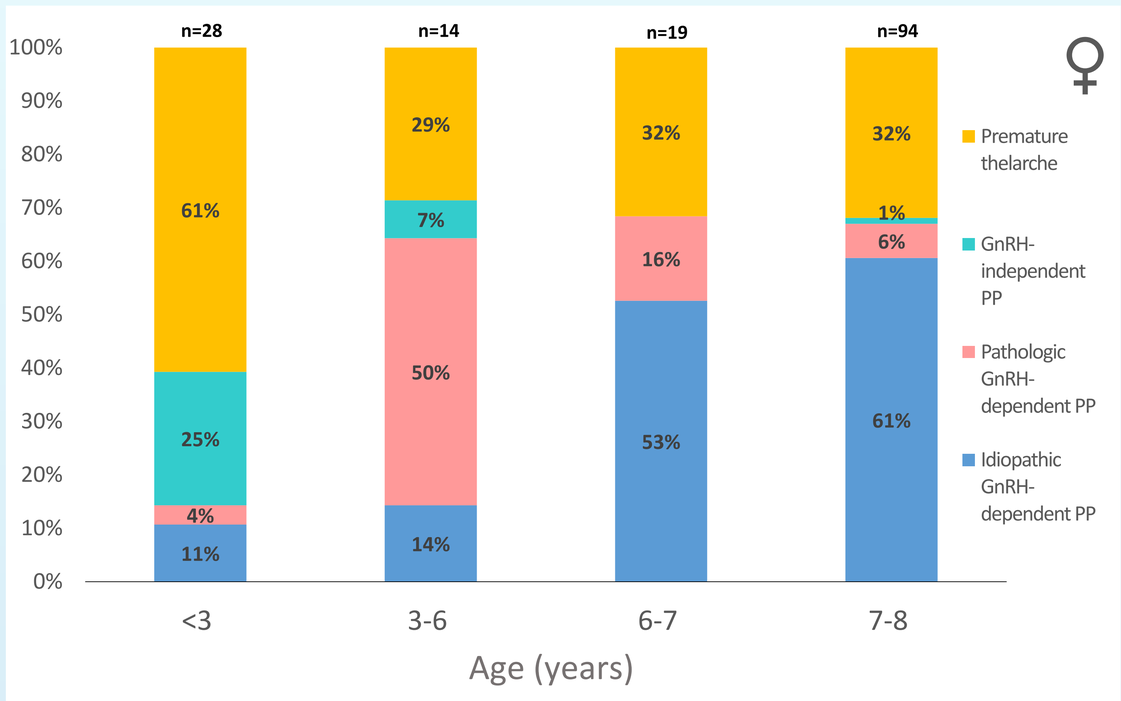

Figure 3. Causes that underlie precocious puberty in girls at different age groups.

Age (years)	<3	3-6	6-7	7-8
Proportion of girls with brain MRI scan available	3/4 (75%)	9/9 (100%)	8/13 (62%)	43/63 (68%)
Pathological findings in MRI	1/3 (33%)	7/9 (78%)	3/8 (38%)	6/43 (14%)

Table 2. MRI coverage in girls with GnRH-dependent PP. Patients are classified based on age at presentation.

- The proportion of brain MRI scan performed in different age groups in girls with GnRH-dependent PP is presented in Table 2. The pathological findings were:
  - a hamartoma in 7 patients
  - other benign tumor in 3 patients (e.g. astrocytoma)
  - partial agenesis of the corpus callosum in 2 patients
  - hydrocephalus in 1 patient
  - other structural brain abnormalities in 4 patients
- In boys, a brain MRI scan was performed in 10/11 (91%) with GnRH-dependent PP
  - 8 boys (80%) had a pathological finding; 4 hamartomas, 2 other benign tumors, 1 malignant tumor and 1 other finding
- The study included 21 adopted girls, of whom 18 had idiopathic CPP, 2 had premature thelarche and 1 had early menarche

Conclusions

- Almost one third of patients with idiopathic CPP had a positive family history of early puberty. These families are currently being enrolled to our genetic study.
- MRI scan was not performed to all patients with PP. This may reflect the implementation of national guidelines that allow tolerance in the cut-off limits if either of the parents had been an early maturer.
- As much as 14% (95% CI, 7%-27%) of 7-8-year-old girls with GnRH-dependent PP had pathological brain MRI findings lending credence to the use of current cut off age limit of PP (5).
- Our study confirmed that a boy with CPP, needs thorough endocrine examination
- Although thelarche is predominant in girls under 3-years-of-age, every third girl has on an organic etiology behind the PP
- In support of previous findings (6), adoption emerged as a negative predictor of an organic cause for PP

References

1. Latronico, A.C *et al.* Lancet Diabetes Endocrinol. 2016, 4(3), 265-274
2. Ojajärvi,P. (1982) The Adolescent Finnish Child. PhD thesis. University of Helsinki
3. Fuqua,J.S. J.Clin.Endocrinol.Metab., 2013, 98(6), 2198-2207
4. Oerter,K.E *et al.* J.Clin.Endocrinol.Metab., 1990, 71(5), 1251-1258
5. Carel,J.C. *et al.* Pediatrics 2009, 123(4), e752-62
6. Mogensen,S.S. *et al.* PLoS One. 2012;7(1):e29829

55ESPE 780--P2
Pituitary and Neuroendocrinology
Heta Huttunen
DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS