Editorial

Wieland Kiess*, Julia Hoppmann, Julia Gesing, Melanie Penke, Antje Körner, Jürgen Kratzsch and Roland Pfaeffle

Puberty – genes, environment and clinical issues

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Introduction

In the context of human development and human lifespan puberty is defined as the transition period from childhood to adulthood. During puberty dramatic and substantial changes with respect to somatic, mental, behavioral and cognitive as well as social, psychological and economic dimensions occur in the individual. At the same time, the individual recognizes the group and the society in which he or she lives in new dimensions and a broader context.

Somatic development, growth acceleration and deceleration occur during pubertal development. In females, menarche occurs during puberty and in males, an increase in testicular volume is testimony to the fact that the individual is indeed becoming fertile. The onset and progression of puberty, i.e. the speed with which an individual will accomplish fecundity and fertility and complete maturation, has been found to be determined by genetic variants of a number of genes. Some of these genes encode neuropeptides, neurotransmitters and their receptors and signaling components that serve as a clock and time keeper in the central nervous system [1–3]. In addition to the intrinsic factors that determine the onset and progression of puberty in the individual, external or extrinsic factors also play a substantial role in regulating puberty and pubertal development. Extrinsic factors include cultural, psychological, nutrition-related and environmental chemicals. Amongst chemicals occurring in, for example, plastic wrappings, toys, water and soil, the so-called endocrine-disrupting chemicals are suspected not only to influence pubertal development but also to influence gender identity, the development of internal and external genitalia, metabolic health and neurocognitive development [4].

Precocious and late puberty are often cause for concern for patients, parents, families and peers. Often, late puberty is related to late and/or slow development which occurs constitutionally and has a strong genetic component: often, children who enter puberty late have parents who have done so as well. Importantly, a large number of chronic diseases may slow puberty onset and/or progression. Cystic fibrosis, chronic rheumatoid diseases, inflammatory bowel disease and renal, cardiac and pulmonary disorders may all impair pubertal development [2]. In this issue of our journal, excellent reports by experts in this field are presented that increase our knowledge in regard to several aspects of puberty and modulation of puberty progression.

Early or late pubertal onset

As has been mentioned above, pubertal maturation in both girls and boys occurs earlier than was previously considered normal. There are many causes that have been suggested to account for earlier maturation. Epidemiologic studies point to genetic variants as the most important factors contributing to the variability in the onset of puberty. The association of high fat content (BMI) with earlier puberty in girls has been proved. In boys, the relationship between BMI and the onset of puberty is less clear. The relationship between BMI and onset of puberty may be mediated by many factors, such as leptin and kisspeptin, changes in the availability of steroid hormones and environmental – i.e. mainly chemical – exposures [5, 6]. Recently, there have been genome-wide meta-analyses examining the onset of puberty and anthropometric traits that may provide insight into the relationships between BMI, height velocity and pubertal timing. Epigenetic modification might add to these classic genetic influences [5].

In a rare case of a patient with the 22q13 deletion syndrome or Phelan-McDermid syndrome, the group from Athens, Greece, elegantly refers to early onset of puberty in this condition and argues that the pubertal onset might be related to the genetic variant which is present in this patient. Phelan-McDermid syndrome is a neurodevelopmental disorder associated with developmental delay, hypotonia, delayed or absent speech, autistic-like behavior, normal to accelerated growth and

dysmorphic faces. The occurrence of central precocious puberty (CPP) in a boy diagnosed with Phelan-McDermid syndrome is reported in this manuscript. At the young age of 1 year, the patient presented an increased testicular volume for his age, bone age advancement and growth acceleration. Stimulated gonadotropin levels demonstrated a premature activation of the hypothalamic-pituitary-gonadal (HPG) axis. CPP was treated with gonadotropin-releasing hormone (GnRH) analog. Molecular diagnosis with array-comparative genomic hybridization (CGH) revealed a major deletion of 5.8 Mb at the 22q13 chromosomal region and a 25 kb duplication at the 9q34.3 region that included the NOTCH-1 gene. On the background of 22q13 deletion syndrome and data from animals on the effect of abnormal NOTCH-1 gene expression on kisspeptin neuron formation, it is quite likely indeed that there is a role of Notch signaling in the premature activation of the hypothalamic-pituitary gonadal axis [7].

Endocrine-disrupting chemicals

Reports on the secular trend of pubertal onset indicate a recent earlier start especially in girls. Endocrine-disrupting chemicals such as bisphenol A (BPA) which possesses estrogenic activity might cause early onset and/or rapid progression of puberty. The objective of the study by Supornsilchai et al. in this issue of our journal was to find out whether or not there was an association between BPA exposures and urinary levels and advanced puberty. In a cross-sectional study in patients with advanced puberty anthropometric measurements, estradiol, basal and gonadotropin releasing hormone (GnRH)-stimulated follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels, uterine sizes, ovarian diameters and bone ages were obtained. Urinary BPA concentrations were analyzed by ultra-performance liquid chromatography-tandem mass spectrometry (UPLC/MSMS). It was found that the median-adjusted BPA concentration in the advanced puberty group was higher than in control groups. Additional data from this study seem to confirm that indeed BPA exposure was related to an earlier age at onset of puberty especially in obese girls [4].

Treatment of precocious puberty

Triptorelin is an established treatment for CPP as 1- and 3-month formulations. However, the current Triptorelin 22.5 mg 6-month formulation is approved for prostate cancer therapy only. Therefore, the group from Chile carried out an efficacy study in patients with CPP. The primary objective was to measure the efficacy in achieving LH suppression to pre-pubertal levels after 6 months of treatment. The study is an international, non-comparative phase III study over a total duration of 48 weeks. Eighteen medical centers in the US, Chile and Mexico participated. Forty-four treatment-naïve patients (39 girls and five boys) aged at treatment start 2–8 years for girls and 2–9 years for boys with an advancement of bone age over chronological age ≥ 1 year were included. Triptorelin was administered intramuscularly twice at an interval of 24 weeks. LH, FSH (basal and stimulated), estradiol (girls), testosterone (boys), auxological parameters, clinical signs of puberty and safety were assessed. Forty-one patients (93.2%) showed pre-pubertal LH levels (stimulated LH ≤ 5 IU/L) at month 6 and maintained LH suppression through month 12. The percentage of patients with LH suppression exceeded 93% at each time point and reached 97.7% at month 12. The authors conclude that the Triptorelin 6-month formulation was safe and effective in suppressing the pituitary-gonadal axis in children with CPP. The extended injection interval may improve compliance and increase comfort in the management of CPP. Indeed, pain and injection site discomfort are important concerns when treatments of precocious puberty are assessed and these findings might prove very important and of high clinical relevance for children with precocious puberty [8].

How does one monitor treatment success biochemically? In an important report by one of the world experts in the field, Dr. Peter Lee from the USA, the suitability of using basal LH levels to monitor GnRH agonist treatment and to determine optimal transition from 1-month to 3-month formulations is being reported via a post hoc analysis of a randomized, open-label, 6-month study.

In this report, 42 children with CPP pretreated with 7.5-, 11.25- or 15-mg 1-month leuprolide formulations were randomized to 11.25- or 30-mg 3-month leuprolide. Basal LH/peak-stimulated LH levels were measured at weeks 0, 4, 8 and 12. Positive/negative predictive values and sensitivities/specificities were determined for basal LH versus LH-stimulation results. Pretreatment with any 1-month formulation largely did not affect continuation of suppression after transitioning to 3-month formulation (mean peak-stimulated LH levels remained < 4 IU/L). Basal LH predicted suppression escape (basal LH-level cutoff ≥ 0.6 IU/L predicted 70% of those failing suppression) [9].

Summary

Intrinsic, mainly genetic, as well as extrinsic, for example, endocrine-disrupting chemicals, factors modulate and direct pubertal onset and progression in humans. As to treatments, the clinical needs, the potential benefits for the patient but also the relative and potential harm that can be associated with injection pain and discomfort have to be considered. Appropriate biochemical monitoring and careful counseling of the affected patients and their families are mandatory. We are glad that our authors have addressed important issues of the clinical aspects of puberty and puberty onset and hope that publication of these reports will improve patient care and stimulate further research in the field.

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***Corresponding author: Prof. Wieland Kiess,** MD, Hospital for Children and Adolescents, Centre for Paediatric Research, Department of Women and Child Health, University of Leipzig, Liebigstr. 20a, 04103 Leipzig, Germany, Phone: +49-341-9726000, Fax: +49-341-9726009, E-mail: wieland.kiess@medizin.uni-leipzig.de
Julia Hoppmann, Julia Gesing, Melanie Penke and Roland Pfaeffle: Hospital for Children and Adolescents, Centre for Paediatric Research, Department of Women and Child Health, University of Leipzig, Leipzig, Germany
Antje Körner: Hospital for Children and Adolescents, Centre for Paediatric Research, Department of Women and Child Health, University of Leipzig, Leipzig, Germany; and Leipzig University Medical Center, IFB Adiposity Diseases, Leipzig, Germany
Jürgen Kratzsch: Institute of Clinical Chemistry, Laboratory Medicine and Molecular Diagnostics, University Hospital Leipzig, Leipzig, Germany