

DELAYED PUBERTY AND HYPOGONADISM: INSIGHTS FROM SINGLE GENE DISORDER

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The timing of pubertal onset is controlled by both genetic and environmental factors. Observations from monozygotic twins indicate that 70-80% of the pubertal timing can be explained by heritable factors and only 26% by environmental influence. Traditionally, hypogonadotropic hypogonadism (HH) is classified into two groups; anosmic isolated HH, IHH (Kallman syndrome (KS) and normosomic Idiopathic HH (nIHH). The first gene discovered in a single patient with KS associated with Xp21 deletion was the *KALI* gene, which encoded the protein, anosmin-1, essential for olfactory guidance system for GnRH neurons. Since this first discovery at 1991, several genes were reported in patients with HH that are involved in puberty and reproduction. Mutations in Fibroblast growth factor receptor-1 (FGFR-1) and its ligand FGF-8 were described in patients with KS suggesting that these 2 genes have a role in GnRH neuronal migration, maturation and survival. In 2003, the G-coupled receptor-54 (*GPR-54*) and its ligand, *KISS-1*, were firstly identified in HH patients. These two genes were shown to be crucial for pubertal onset and reproduction. In 2006, two new genes that are associated with circadian clock were described in nIHH patients, Prokinetkin 2 (*PROK2*) and its receptor *PROKR2*. Recently (2009) mutation in the neurokinin and neurokinin receptor were reported in hypogonadic patients. All the above-mentioned genes account for only 30% of the cases of HH, suggesting that additional genes that are involved in puberty and reproduction yet to be identified. Bigenic inheritance was described in some patients indicating multigenic inheritance in HH. Clinical observations in affected patients with HH revealed variable phenotypes. It has been shown that several carriers are asymptomatic, both anosmic and normosomic HH were described among subjects with the same mutated gene, partial spontaneous puberty, reversal of HH after discontinuing androgen therapy and late acquired hypogonadism in subjects with normal puberty and fertility were shown. A novel approach for studying the timing of puberty involved genome-wide-association studies (GWAS). This review summarized recent advances regarding the genetic control of pubertal timing and present areas of future investigation.

The consensus statement on precocious puberty

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Objective: The Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology convened a consensus conference to review the clinical use of GnRHa in children. The outline of the consensus will be presented.

Clinical criteria for therapy: Progressive pubertal progression and growth acceleration should be documented over a 3-6 months period prior to GnRHa treatment initiation, unless the child is Tanner \geq III.

Age criteria: Girls with onset of CPP before 6 years will benefit most from the treatment, while after 6 years the decision should be individualized. Treatment should be considered in all boys with onset of progressive puberty before 9 years, who have compromised height potential.

The hormonal and ultrasound criteria for treatment will be discussed, as well as the need for CNS imaging in case of CPP.

The presentation will address the issues of monitoring during therapy, adverse events, factors that should be used to guide treatment discontinuation and long-term outcome.

Conclusions: The efficacy of GnRHa to increase the adult height is undisputed only in early onset CPP. Other key areas, such as the psychological effects of CPP and their modulations by GnRHa, need further study. In fact, few rigorously conducted and controlled prospective studies have been performed with GnRHa, such as promotion of weight gain or long-term diminution of bone mineral density. Use of GnRHa in conditions other than CPP requires further investigation and cannot be routinely suggested.

Treatment of Central Precocious Puberty: What is new?

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Central precocious puberty (CPP) refers to early activation of the hypothalamic-pituitary-gonadal (HPG) axis. It occurs much more frequently in girls than in boys, in whom it is usually idiopathic. Known risk factors for CPP include congenital or acquired CNS insults, as well as international adoption. The goals of therapy are to restore prepubertal sex steroid levels, halt pubertal development, slow the rate of skeletal maturation and ultimately improve adult height. Gonadotropin releasing hormone analogs (GnRHa) have an excellent track record of safety and efficacy and are the treatment of choice for CPP worldwide. The mainstay of therapy has typically involved intramuscular injections. An alternative delivery system has emerged in the form of a subcutaneous implant that releases the potent GnRHa histrelin in a continuous fashion for at least a year. Following an initial pilot study in 11 girls with CPP, a one-year trial of the histrelin implant was conducted in 36 subjects, 20 of whom were naïve to GnRHa treatment. Of the original cohort, 31 subjects had a new implant placed for a second year of treatment, and 22 have received a third. The histrelin implant causes profound suppression of the HPG axis, with a resultant decrease in the rate of bone age advancement and an increase in predicted adult height. Although well tolerated overall, minor implant site reactions are common, and occasional issues with implant localization and breakage during explanation have occurred. Preliminary experience indicates rapid recovery of the HPG axis once the histrelin implant is removed. Minimal information is available regarding adjunctive therapy in children with CPP on GnRHa. Although small, uncontrolled studies have suggested a modest benefit from the addition of growth hormone or oxandrolone to GnRHa in children with slow growth, more data are needed. Long-term follow-up of outcomes including adult height, reproductive function and bone mineral density in children treated with GnRHa are essential. Continued investigation of new therapeutic approaches will enhance knowledge and optimize treatment of children with CPP.