

height in z-scores corrected for target height z-scores was decreased in both genders with girls being more affected than boys. Height velocities were correlated with insulin like growth factor (IGF)-I and IGF binding protein (IGFBP)-3 z-scores and with the height z-scores corrected for target.

The authors affirmed normal prenatal growth in boys and girls with galactosemia, but decreased height and weight growth velocities. In addition they stated that predicted final height was less than target height in most patients after birth. The authors' review of the literature suggested a variety of variable findings in at least 3 other studies, some showed decreased height-for-age but final height within normal limits,¹ microcephaly,² and reduced birth weight in affected neonates.³ The authors speculated that possible risk factors for abnormal growth include either intrinsic or diet-related factors, decreased mean IGF-I and IGFBP-3 concentrations and/or hormonal factors.

Panis B, Gerver W, Rubio-Gozalbo ME. Growth in treated classical galactosemia patients. *Eur J Pediatr.* 2007;166:443-6.

Editor's Comment: *Galactosemia may be a more common finding in genetics clinics than in endocrine*

clinics. The growth data which Panis reported in a large group of children with classical galactosemia would not usually result in a referral to a pediatric endocrinologist for evaluation. It would have been interesting had these investigators provided a little more information especially in regard to how they determined predicted adult height. There is no mention of bone ages being performed in these individuals. It is easy to speculate that girls with galactosemia and ovarian dysfunction would most likely have lower height z-scores than the normal population. Despite its shortcomings, this paper presented important information which suggests when children with classical galactosemia are evaluated in either genetics or metabolic clinics, there should not be an expectation for short stature or failure to thrive, at least when the diet is followed consistently. Thus short children with classical galactosemia should be evaluated thoroughly for other hormonal causes of growth failure.

William L. Clarke, MD

References

1. Waggoner DD, Buist NR, Donnell GN. *J Inherit Metab Dis.* 1990;13:802-18.
2. Schweitzer S, Shin Y, Jakobs C, et al. *Eur J Pediatr.* 1993;152:36-43.
3. Hsia DY, Walker FA. *J Pediatr.* 1961;59:872-83.

Height Screening During the Primary School Years: Evidence Behind Practice?

Height and weight monitoring has long been a fundamental aspect of pediatric care as indicators of both health and possible underlying pathology. Unfortunately, delays in diagnosis and treatment of underlying growth problems are frequently observed. The optimal strategy remains elusive, as the standard cut-offs between normal and abnormal and the recommended growth screening practices vary widely. For example, the Child Health Subcommittee of the UK National Screening Committee recommended a cut-off of 0.4th centile and a single height and weight measurement at or around the time of school entry for screening.¹

Fayter et al performed a systematic review of the effectiveness and economic modeling of height screening in primary school aged children to identify height-related conditions (focusing on stature, not obesity). They collected all studies from database inception (1974) to July 2005 that measured child height as part of a population-level assessment of children aged 4 to 11 years in Western Europe, North America, Australia and New Zealand (excluding aboriginal populations). All study designs, except case reports, were accepted.

Effectiveness was assessed from the number of cases of all conditions detected. Meta-analysis of diagnostic yield data was precluded by the heterogeneity of child age, reference charts and screening methods used; thus, effectiveness data were limited to descriptive summaries. Twelve studies of height screening programs provided diagnostic yields of new cases and measured 45% to 90%

of eligible children. A single measurement at school entry identified new cases of underlying growth conditions at rates of 0.54 to 0.56 per 1000 children screened.

Economic modeling was based on pooled raw data from 12 diagnostic yield studies, providing probability distributions for new case detection of each included condition. Lifetime costs and outcomes were modeled, following NICE guidelines, and included screening, referral, and treatment costs reflatd to 2006 values. A cost/QALY analysis (a QALY = a year of life, adjusted for its quality or perceived value) compared height screening at school entry (age 5 years) versus no screening (diagnoses found later in clinical practice). QALY estimates, based on the literature and an expert clinical panel, assumed early detection and screening would provide double the QALY gains than later detection from no screening. Using the number of 5-year-old children in England and Wales, the model found an incremental cost-utility of height screening at £9,900 (~\$19,800 US) per QALY. Probabilistic sensitivity analysis found that all of the model's data distributions fell below the UK willingness to pay thresholds of £30,000 per QALY. Thus, the authors concluded that height screening in primary school aged children is diagnostically useful and economically justifiable.

Fayter DA, Nixon J, Hartley S, et al. Effectiveness and cost-effectiveness of height screening programmes during the primary school years: a systematic review. *Arch Dis Child.* 2007 May 2. [Epub ahead of print]

Editor's Comment: *It is striking that such financial analyses are now needed to justify growth screening, a fundamental tenet of pediatric care. However, as highlighted by this paper, many of the considerations remain elusive. What is the optimal height cut-off to identify likely pathology? What is the optimal screening paradigm? Serial height measurements will capture cases of growth deceleration before they become severe enough to cross the single height cut-off for pathology, but how frequent and how many are needed to balance improved sensitivity with increased cost? What is the actual cost of missed or delayed diagnoses and how are QALYs estimated, especially since the impact of short stature on quality of life remains so controversial? And what about the cost of height monitoring itself? Height*

measurements in the United States are performed as part of routine pediatric well child care,² and the cost of a stadiometer spread across the patient population is so negligible that it seems virtually free. The only real cost is the time to accurately measure the child and plot the measurements on the appropriate growth chart. With the increasing pressures to expedite patient flow faster and faster, time may be the most expensive aspect of growth screening.

Adda Grimberg, MD

References

1. National Screening Committee. Child health sub-group report: growth disorders. Leeds: National Screening Committee; 2004.
2. American Academy of Pediatrics Policy Statement - Committee on Practice and Ambulatory Medicine. Pediatrics. 2000;105:645.

Histrelin Subdermal Implant in Central Precocious Puberty

This important article describes efficacy and safety data related to the use of a single annual subcutaneous implantation of a gonadotropin-releasing hormone analogue (GnRHa) to induce pituitary gonadotropin suppression in children with central precocious puberty. Histrelin provides a continuous slow release at an average rate of 65 µg/d of GnRHa. Its use as a single yearly implant has previously been shown to effectively suppress LH, FSH and testosterone secretion in adult males with prostate cancer.^{1,2} This report is the first in children with precocious puberty.

The procedure of implantation will require more detailed examination with wider clinical use. A pediatric surgeon is required to perform this procedure and in this study, local or general anesthetic or sedation was used. There is no comment about any practical difficulties with the implantation in terms of interference with daily activities such as sports and recreation, or whether the implant became dislodged in some patients.

Eugster EA, Clarke W, Kletter GB, et al. Efficacy and safety of histrelin subdermal implant in children with central precocious puberty: A multicenter trial. J Clin Endocrinol Metab. 2007;92:1697-704.

Editor's Comment: *The data on sex steroid, LH and FSH evaluation are impressive and clearly show that effective suppression of gonadotrope function occurs for 12 months after a single subcutaneous implantation. The choice of patients may need to be individualized and an implantation technique which avoids general anesthetic would clearly be preferable. Longer term studies to assess recovery of the pituitary-gonadal axis following discontinuation of treatment are important. This first report in children is encouraging and may eliminate the discomfort of monthly or three-monthly injections as currently practiced.*

Martin O. Savage, MD

References

1. Schlegel PN, Kuzma P, Frick J, et al. Urology. 2001;58:578-82.
2. Chertin B, Spitz IM, Lindenberg T, et al. J Urol. 2000;163:838-44.

Hypogonadotropic Hypogonadism—Mutations and Phenotypes

Isolated hypogonadotropic hypogonadism (IHH) has been associated with mutations in 7 genes to date (Table). The products of the genes encoded by *KAL1*, *FGFR1*, *PROK2*, *PROKR2*, and *NELF* assist in the regulation of neural movement within the CNS—particularly the migration of olfactory and gonadotropin releasing hormone (GnRH)-containing neurons from the olfactory placode during early embryogenesis. Mutations in these genes result in abnormalities of GnRH secretion and the reproductive endocrine system (delayed adolescence, hypogonadotropism) and the sense of smell (hyposmia, anosmia), and those afflicted often display other neurologic (bimanual synkinesia) and somatic (renal agenesis) anomalies. These traits

are transmitted in an autosomal dominant manner often with incomplete penetrance and substantial inter- and intrafamilial variability in clinical manifestations. Mutations of *GPR54* limit release of GnRH while those of the *gonadotropin-releasing hormone receptor (GNRHR)* impair its function at the gonadotroph membrane. These disorders are transmitted in an autosomal recessive manner and are not associated with other specific clinical or anatomic abnormalities.

Intrigued by the variable clinical manifestations of IHH, Pitteloud and colleagues examined the genotype of 2 families in which single gene defects thought to have resulted in IHH had been previously identified. In pedigree #1, a 21-year-old male with IHH and