

Ono M, Chia DJ, Merino-Martinez R, Flores-Morales A, Unterman TG, Rotwein P. Signal transducer and activator of transcription (stat) 5b-mediated inhibition of insulin-like growth factor binding protein-1 gene transcription: a mechanism for repression of gene expression by growth hormone. *Mol Endocrinol.* 2007;21:1443-57.

**Editor's Comment:** *Through a well constructed series of experiments, Ono et al clearly showed that GH inhibits IGFBP-1 expression via activated Stat5b and FoxO1. However, the exact mechanism of FoxO1 inhibition by Stat5b remains elusive; FoxO1 protein degradation, nuclear exclusion and impaired DNA binding ability were all ruled out, as was direct protein-protein interaction between Stat5b and FoxO1. Nonetheless, this paper expands our thinking along 2 lines. First, GH, via activated Stat5b, not only induces gene expression (eg. IGF-I), but also represses transcription of other genes, such*

*as IGFBP-1. Thus, the genetic response to GH/Stat5b signaling is a richer compilation of coordinated alterations than previously appreciated. Second, the mechanism whereby IGFBP-1 expression is repressed by GH is clearly distinct from that of insulin (activated Akt phosphorylating FoxO1, thereby sequestering it out of the nucleus and impairing its ability to transcribe IGFBP-1'). Although we are used to thinking of GH as counter-regulatory to insulin, in certain circumstances, like IGFBP-1 expression as shown here, the two hormones can act synergistically because they effect the same molecular change through separate pathways.*

Adda Grimberg, MD

#### Reference

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## GH Neurosecretory Dysfunction and Cranial Irradiation

The group of Shalet in Manchester, UK has made fundamental contributions to the understanding of the broad range of endocrinopathies which may follow cancer therapy in children. In terms of clinical practice, deficiency of growth hormone (GH) following cranial irradiation constitutes an important entity of which all pediatric endocrinologists need to be aware. Prophylactic cranial irradiation for leukemia has been largely replaced by use of intrathecal cytotoxic agents. However, targeted high-dose radiotherapy (RT) for brain tumors outside the hypothalamic pituitary region, such as medulloblastomas, remains an essential and potentially life-saving therapy.

The relationship between the dose of RT and the frequency of subsequent GH deficiency has been clearly established. This article critically considers whether patients who have normal GH responses to pharmacological testing may have a more subtle defect of physiological pulsatile GH release, ie, so-called GH neurosecretory dysfunction. The presence of this 'defect' of probably hypothalamic origin was assumed when subnormal pulsatile secretion was reported

during adolescence, particularly after low-dose RT in several studies.

Darzy KH, Pezzoli SS, Thorne M, Shalet SM. Cranial irradiation and growth hormone neurosecretory dysfunction: A critical appraisal. *J Clin Endocrinol Metab.* 2007;92:1666-72.

**Editor's Comment:** *The combined groups of Shalet and Thorne have performed extremely detailed assessments of physiological GH secretion (cluster analysis) in adult patients, most of whom received RT during childhood, and in normal controls. Such a study would have been impossible in pediatric subjects. The hallmarks of neurosecretory dysfunction, ie, normal GH secretion, after provocation compared with decreased spontaneous secretion were not seen. This helpful finding effectively dismisses this abnormality from potential sequelae of cranial RT in childhood. The peak GH concentration after a pharmacological provocation test can be taken as a realistic index of somatotrope secretory capacity. Performing physiological studies is unlikely to add further clinically relevant information.*

Martin O. Savage, MD

## Growth in Treated Classical Galactosemia Patients

Panis and co-workers studied height and weight growth over a period of 2 years in a group of 40 Dutch children and adolescents with classical galactosemia. These subjects (13 boys, 27 girls, median age 7.8 years, range 3 to 17 years) had the diagnosis established in the neonatal period by galactose-1-phosphate-uridylyltransferase (GALT) and enzymatic studies in erythrocytes. Of the 40 subjects, 31 were prepubertal, and 5 had reached Tanner stage 5. Urinary galactose and galactitol concentrations and GALT levels in the erythrocytes were measured during the study and all were within the

range of treated patients. Prenatal growth was evaluated by obtaining length, weight, and head circumference data from infant welfare centers or from parents. The results, corrected for gestational age, were within normal limits for the Dutch population. Yearly, for 2 successive years, postnatal growth was evaluated by z-scores and corrected for target age. Mean height growth velocity was  $0.87 \pm 1.2$  (range  $-0.4$  to  $3.6$ ) for boys and  $-0.89 \pm 2.1$  (range  $-2.5$  to  $3.7$ ,  $p=0.047$ ) for girls. Weight growth velocity in z-scores was  $0.91 \pm 1.6$  (range  $-0.8$  to  $4.2$ ) for boys and  $-0.74 \pm 1.3$  (range  $-3.1$  to  $2.3$ ,  $p=0.008$ ) for girls. Mean

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,<sup>1</sup> microcephaly,<sup>2</sup> and reduced birth weight in affected neonates.<sup>3</sup> 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

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## 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 0.4<sup>th</sup> centile and a single height and weight measurement at or around the time of school entry for screening.<sup>1</sup>

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]