Endocrine: Short stature and effect of Human Growth Hormone (HGH) for children with Spina Bifida (SB)

Background


At present the primary effort to reduce the incidence of obesity among individuals with SB is diet and exercise. Unfortunately, the rate of obesity among individuals with SB is between 50-75%, other interventions to improve linear growth velocity and improve the health and wellbeing. There are many parameters that are used to define and diagnose obesity. All of which may be difficult to apply to individuals with SB. Height and or length measurements are difficult due to disproportionate lower extremity growth, contractures of lower extremities, inability to stand for measurements or lie straight and flat on a stadiometer due to scoliosis, kyphosis, or physical discomfort. This is important since inaccurate measures of body length can affect the calculation of the Body Mass Index (BMI). Arm span, humeral length, mid-arm circumference, waist circumference are all surrogates in some form to calculate BMI. One possible measure of obesity has been concentration of nocturnal serum leptin. Trollman et. al. measured spontaneous nocturnal leptin secretion in children with SB and growth hormone deficiency. 32 prepubertal children (10 SB with GH deficiency, 10 non-SB with GH deficiency, and 12 children with normal variant stature scores (similar to Z-scores). The average ages were 6.2, 7.6, and 7.6 years respectively. The researchers checked nocturnal leptin levels over 10 hours at 20 minute intervals. They found that the average leptin concentration didn’t correlate with BMI in SB patients and their nocturnal leptin secretion was very different from the two control groups. They observed no morning decline in leptin secretion among SB group compared to the two others. They concluded that there was hypothalamic dysregulation of leptin secretion among children with SB. (Trollman R, Dorr HG, Groschul M, Blum WF, Rascher W, Dotsch J. Spontaneous nocturnal leptin secretion in children with myelomeningocele and growth hormone deficiency. Hormone Research 58(3): 115-9, 2002.)

If the height of an individual with SB could be improved, the distribution of adipose tissue would be redistributed, or reduced with improvements of all physical factors associated with obesity, less risk of subsequent medical problems, and a substantial improvement in quality of life.

What is known about the use of HGH for children with SB?

1. Rotenstein and Bass selected 20 patients with SB (12 males) who were growth hormone deficient and treated for variable lengths of time with HGH (0.3mg/kg/wk) until they reached
90% of predicted adult height. Lesion level: Lumbar (16), sacral (4), and 19 of 20 had shunted hydrocephalus. The control group were general population age-matched controls and untreated adults with SB. For 15 of 20, when treatment was stopped at 90% adult height, their stature were greater than the 3rd percentile on growth charts were less overweight (based BMI), had better growth than untreated SB. (Rotenstein D, Bass AN. Treatment to near adult stature of patients with myelomeningocele with recombinant human growth hormone. Journal of Pediatric Endocrinology. 17(9): 1195-2000. 2004 Sep.)

2. Trollman, Strehl, Wenzel, and Dorr evaluated the effect of HGH on GH deficient children with Myelomeningocele. This study of seven children with SB and GH deficiency (all had GH stimulation tests, overnight measurements of GH secretion), 5 males, 2 females, average age 6.6 years, all with shunted hydrocephalus, who were treated for an average of 38 months with HGH. The group measured growth, neurologic, and orthopedic status. They found that there was an increase in supine length, and arm span with arm span having a greater growth. The supine length and arm span were significantly greater than pretreatment measures. On 2 of the seven children, symptomatic tethering of the spinal cord developed with progression of scoliosis. (Trollman R, Strehl E, Wenzel D, Dorr HG. Does growth hormone enhance growth in growth hormone deficient children with myelomeningocele? Journal of Clinical Endocrinology and Metabolism. 85(8):2740-2743. 2000 Aug.)

3. Another study by Rotenstein and Reigel considered HGH treatment of children with neural tube defects comparing duration of treatment (6 months to 6 years). This retrospective review of the data for 22 children with SB treated with HGH (0.3mg/kg/d) evaluated growth rate and length standard deviation score found that the length standard deviation scores was greater than 0.2 SD for 64%. Growth rate increased through all 4 years but the growth rate at 6 months was highest and showed the highest chance of success.

4. Rotenstein and Breen using data from the National Cooperative Growth Study database of 106 patients with SB at 56 centers. Of these children, 56 were male, mean chronological age was 6.5 years, mean height-age was 3.7 years and 81 were prepubertal at enrollment. Prior to treatment the mean growth rate was 4.5 (+/- 3.7 cm/yr), mean height standard deviation score was -4.0 (+/- -1.2), GH level on stimulation test was less than 10 mcg/l for 71% and less than 7 mcg/l for 49%. After treatment, the growth rate among those who were still prepubertal was 8.5 (+/- 3.3 cm/y). The increased growth rate extended through year four and investigators concluded that both growth rate and length standard deviation improved with HGH treatment. Rotenstein D, Breen TJ. Growth Hormone treatment of children with meningomyelocele. Journal of Pediatrics. 128(5, pt. 2) 528-31, 1996 May.

Overall Outcomes

1. Primary outcomes
   a. Improve linear growth to improve distribution of adipose tissue.
   b. Reduce BMI with goal to decrease rate of obesity among individuals with SB.

2. Secondary outcome
   a. Improve quality of life by improving strength, mobility, body image, and health.
   b. Reduce morbidity and mortality secondary to obesity.

3. Tertiary outcomes
a. Improve quality of life by decreasing need for obesity-related illnesses and interventions.

Gaps in understanding:

1. While linear growth is impacted by effects of the myelomeningocele, at which age does the length become most affected (toddler years, prepubertal growth spurt, puberty)?
2. At what age is the short stature evaluated initiated?
3. Does HGH improve lipid or bone metabolism?
4. Does HGH result in a positive change in adult height sufficient to show improved self-esteem, reduced obesity, better muscle strength, bone density, and rehabilitation potential?

INFANCY

Clinical Questions

1. At what age do pituitary-hypothalamic hormones become affected by Chiari malformation, hydrocephalus, or placement of shunts?
2. Could growth during infancy and toddler years be improved by use of HGH?
3. Does the use of HGH worsen other comorbidities associated with SB? (tethering< scoliosis, muscle tightness, etc)
4. What and when are the appropriate evaluations for use of HGH?

Proposed guidelines for growth and nutrition during infancy

1. Frequent and accurate weight, length, and OFC measurements during infancy
2. Referrals to physical therapy to maximize range of motion, strength, and functional mobility as appropriate for developmental age.
3. Encourage breast feeding and appropriate nutrition.
4. Discuss with the family issues surrounding growth of children with SB.

PRESCHOOL, AND SCHOOL AGE

Note: Toddler was left out of the headers. In the slides Toddler is included in this group. Please note whether it needs to be combined with Infancy above.

Clinical Questions

1. While linear growth is impacted by effects of the myelomeningocele, at which age does the length become most affected (toddler years, prepubertal growth spurt, puberty)?
2. At what age is the short stature evaluated initiated?
3. Who should do the evaluation, and where should the evaluation be conducted?
4. Which parameters best predict a positive response to HGH?
5. Is HGH only indicated where a growth hormone deficiency is identified?
6. Who should cover the cost of HGH?
7. Are there any limitations regarding who would be eligible: normal development, shortened arm span, minimal skeletal deformities, level of spinal lesion, amount of paresis, syringomyelia, tethered cord, scoliosis, vertebral anomalies, contractures or advanced pubertal development, with or without documented growth hormone deficiency?
8. Does HGH improve lipid or bone metabolism?
9. Does HGH result in a positive change in adult height sufficient to show improved self-esteem, reduced obesity, better muscle strength, bone density, and rehabilitation potential?

**Proposed guidelines for growth and nutrition during preschool through school age**

1. Frequent assessment of growth velocity is recommended.
2. Discussions with the family of the expected height of the child considering the limitations due to myelomeningocele and the expected height based on parent’s height.
3. Discussion of the risks and benefits of GH therapy.
5. Monitoring pituitary function, scoliosis, tethering of spinal cord, growth velocity, and pubertal development.

References: