Abstract. It is estimated that a significant percentage of individuals with spina bifida (SB) are shorter than their age-matched typical peers. Parents of children with spina bifida may ask if human growth hormone is appropriate for their child. This article discusses short stature and the use of human growth hormone among children with SB. This guideline was developed for SB Healthcare Guidelines from the 2018 Spina Bifida Association’s Fourth Edition of the Guidelines for the Care of People with Spina Bifida.

Keywords: Spina bifida, short stature, human growth hormone, obesity, myelomeningocele, neural tube defects

1. Introduction

The incidence of short stature among children with spina bifida is well documented [1–3]. The short stature is primarily due to disproportionate short growth of the lower body segments. Since at one time children with spina bifida were thought to have a shortened life expectancy, lack of physical growth was considered a secondary problem. As duration and quality of life have improved, the awareness of the auxological development of children with spina bifida has increased [4]. The etiology of short stature among children, adolescents, and adults with spina bifida is multifactorial and is a function of inadequate innervation, lack of use of muscles, hip dysplasia, scoliosis, and shortened lower body segments. In general, upper limbs are not affected by the neurological or skeletal anomalies in spina bifida except in patients with symptomatic Chiari malformations [5]. In addition, the majority of children with spina bifida have hydrocephalus. Prior work has demonstrated that hydrocephalus impacts the secretion of pituitary hormones responsible for growth and pubertal development [2]. Multiple studies have demonstrated an increased prevalence of growth hormone deficiency (GHD) in children with spina bifida [4–6]. Perone et al. noted abnormal hypothalamic-pituitary function in children and adolescents with myelomeningocele [6]; it is estimated that approximately 30% of children with spina bifida have GHD [7]. This is important because GHD contributes to abnormal body composition in these individuals that is exacerbated by inactivity, caloric intake, and other factors, increasing the risk of obesity. This can lead to diminished quality of life due to decreased mobility, hyperglycemia, metabolic syndrome, hypertension, type 2 diabetes, skin breakdown, and coronary vascular disease.

There have been multiple studies regarding the use of human growth hormone (GH) for children with spina bifida [8,9]. Recombinant human GH treatment has been used to increase the short-term growth velocity of children with myelomeningoceles without adverse effects on body proportions [8]. In this study, children...
Table 1

| Age group (from guidelines) | Clinical questions that informed the short stature & the effect of Human Growth Hormone (HGH) guidelines |
|-----------------------------|--------------------------------------------------------------------------------------------------|
| 0–11 months                 | At what post-conceptual age do pituitary-hypothalamic hormones become affected by Chiari malformation, hydrocephalus, or placement of shunts? Could growth during infancy and first three years be improved by use of hGH? What and when are the appropriate evaluations for use of hGH? |
| 1–2 yrs. 11 months          | At what post-conceptual age do pituitary-hypothalamic hormones become affected by Chiari malformation, hydrocephalus, or placement of shunts? Could growth during infancy and first three years be improved by use of hGH? Does the use of hGH worsen other comorbidities associated with spina bifida, such as scoliosis, tethered cord, or spasticity? What and when are the appropriate evaluations for use of hGH? |
| 3–5 yrs. 11 months          | While linear growth is impacted by the effects of the myelomeningocele, at which age does the length become most affected (pre-pubertal years, pubertal growth spurt, and puberty)? At what age is the short stature evaluation best initiated? Who should do the evaluation and where should the evaluation be conducted? Which parameters best predict a positive response to hGH? Is hGH only indicated where growth hormone deficiency is identified? Who should cover the cost of hGH? Are there eligibility limitations to hGH treatment, such as: 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? Does hGH improve lipid or bone metabolism? Does hGH result in enough of a positive change in adult height to see improved self-esteem, reduced obesity, better muscle strength and bone density, and rehabilitation potential? |
| 6–12 yrs. 11 months         | While linear growth is impacted by the effects of the myelomeningocele, at which age does the length become most affected (pre-pubertal years, pubertal growth spurt, and puberty)? At what age is the short stature evaluation best initiated? Who should do the evaluation and where should the evaluation be conducted? Which parameters best predict a positive response to hGH? Is hGH only indicated where growth hormone deficiency is identified? Who should cover the cost of hGH? Are there eligibility limitations to hGH treatment, such as: 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? Does hGH improve lipid or bone metabolism? Does hGH result in enough of a positive change in adult height to see improved self-esteem, reduced obesity, better muscle strength and bone density, and rehabilitation potential? |

With growth hormone deficiency showed significant increases in growth velocity without inducing abnormal body proportions. Trollmann et al. also observed that GH treatment provided a substantial gain in height for a group of children with spina bifida, 65% of whom had GHD [9]. In light of the high prevalence of GHD in patients with spina bifida and the demonstratred benefits of GH treatment in GH deficient patients, we offer guidelines for monitoring children with spina bifida for signs of growth failure [10].

1.1. Goals and outcomes

The goals of the guidelines for short stature and the effect of human growth hormone were both practical and aspirational. The primary outcomes of this review and recommendations are to:

- Identify individuals with spina bifida who have growth hormone deficiency
- Improve quality of life by improving lean body mass, strength, mobility, body image and health
- Reduce morbidity and mortality secondary to obesity

With the development of goals and outcomes for short stature and the use of human growth hormone, many questions addressing clinical evaluation and management were raised for further discussion and study (Table 1).

1.2. Methods

The methodology of the development of the guidelines was reported by Dicianno et al. [11]. A small multidisciplinary working group was recruited and convened based on expertise to review previous clinical care guidelines, choose pertinent topics, agree upon
outcome measures, and develop clinical questions and guidance to address this topic for optimal care for people with spina bifida. These questions were vetted by a panel of experts from the Spina Bifida Association and ranked by importance. A literature review pertinent to the topic was conducted from 2002 through 2015 and updated with works published from 2002 to 2015. Two levels of review were conducted. The first level consisted of review of titles and abstracts to eliminate articles that did not address the clinical questions for that guideline. The second level of review involved reading the full text of the article to determine if the work should be included in the literature review for the development of the guideline. The next phase of development was the drafting of the guideline with introduction, outcomes, clinical questions, guidelines and research gaps. These drafts were presented to a committee of working group chairs who served as reviewers and editors for that guideline. The subsequent draft was then submitted for review and comment at a meeting of all guideline writing participants at the national Spina Bifida Association Meeting in March 2015. Nominal Group Technique was used to solicit feedback on individual guidelines [12–16]. This technique allowed for expert opinion to be included for those guidelines where medical evidence was non-existent or was not robust. Participants in this review were able to rate the proposed guideline and provide feedback. Once changes were incorporated, a review was then conducted by a panel of six experts in the field for consistency, redundancy, disability-sensitive language and clarity. The final review was completed by the Spina Bifida Association Steering Committee and was sent for copyediting once approved [11].

2. Results

The Short Stature and Effect of Human Growth Hormone guidelines (Table 2) seek to facilitate identification of children with abnormal linear growth and promote timely referral for further evaluation and treatment if needed. The guidelines recommend examining children at regular intervals and thoroughly documenting physical examination findings so that changes may be tracked over time. This includes not only length/height and weight, but also the presence of any pubertal changes, such as breast development, genital maturation, or the presence of pubic or axillary hair. The guidelines emphasize careful communication with families regarding the findings and concerns. Although short stature is common in children with spina bifida, the use of human growth hormone has specific indications and honest and open discussions with the patient and family are needed prior to any clinical decisions.

3. Discussion

For these guidelines, the desired outcomes are based on improving the lives of individuals with spina bifida by identifying those with growth hormone deficiency, thus permitting treatment in a timely fashion. Because GHD is estimated to occur in as many as 30% of children with spina bifida [7], all health care providers, including those providing primary care, should be aware of its manifestations.

Adult height is known to be limited in those with spina bifida. One study demonstrated that the mean adult height of men with spina bifida was 152.1 ± 13 cm, and in women adult height averaged 141.9 ± 12 cm, far below the average height for healthy adults of 176 cm and 163.5 cm, respectively [18]. Because there are many contributors to growth impairment in those with spina bifida, such as shortened lower body segments, scoliosis, and limb contractures, it may be challenging to identify those with GHD. Biochemical testing for GHD is problematic, due to the limited specificity and a high false positive rate in unscreened populations [19], so universal biochemical testing should be avoided. Instead, identification of a subpopulation with higher a priori risk for the disease is the first step in the evaluation.

Measurement of arm span avoids the issues of abnormal lower segment growth and scoliosis and correlates well with height in healthy children. Arm span has been used successfully to identify children with spina bifida who have GHD [4,5]. Another important concept is height velocity. The hallmark of GHD is not only short stature (or short arm span) but a decreased rate of change. Thus, children with GHD become shorter relative to their peers as time progresses. Repeated measurements of height or arm span at multiple visits allows identification of those with a high risk of having GHD and allows those children to be referred earlier for further evaluation and treatment. In general, earlier institution of treatment for GHD leads to improved long-term outcomes. It is also important to consider the pubertal status of the child. Central precocious puberty is common in children with spina bifida, especially girls. The pubertal growth spurt also occurs early in children with precocious puberty. Although its magnitude may
be limited, the growth spurt may mask the decreased height velocity in children with coexisting GHD and precocious puberty.

After referral to a pediatric endocrinologist, the medical evaluation of growth failure generally includes an assessment for many potential causes of poor growth, including screening for non-endocrine conditions such as celiac disease, inflammatory bowel disease, or electrolyte disorders. Depending on the amount and quality of the growth data, a period of observation to confirm slow height velocity may be required. Endocrine testing usually includes measurement of thyroid function and screening tests of GH secretion such as insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3). Skeletal maturation is assessed by a bone age X-ray. Dynamic testing is usually required for the formal diagnosis of GHD and involves short-term stimulation of GH secretion by administration of two GH secretagogues such as arginine, clonidine, L-DOPA, glucagon, or insulin. Most pediatric endocrinologists consider a peak stimulated serum GH concentration < 10 ng/mL to be consistent with GHD. Random, non-stimulated GH levels are not useful.

In addition to slow linear growth, GHD has a variety of other effects. In otherwise healthy children, growth hormone deficiency clearly causes decreases in bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) at both the lumbar spine and the distal radius [20,21]. Treatment with GH leads to clinically significant improvements in bone density in this population. In a study of young adults with childhood onset GHD, Underwood et al. found low base-line BMD at the lumbar spine. Bone mineral density increased in the treated group by 5.2% vs. 1.3% in untreated controls [22]. Interestingly, data on fracture risk are less clear, with some authors reporting increases in fracture risk in GH deficient adults [23,24] and others showing no differences in fractures compared to healthy adults [25]. There are no good data on fracture risk in
children. In one study of 41 adolescents with GHD who had been treated until they reached adult height, there was no difference in the rate of fractures compared to age-matched controls. However, in those patients who did have a fracture, the lumbar spine BMD was lower than in those who did not fracture [26].

Children with GHD also have clear decreases in muscle mass. When measured by peripheral quantitative computed tomography (pQCT), muscle cross-sectional area was lower in GH deficient children than in healthy controls and increased after two years’ treatment with GH [27]. However, studies in GH deficient children have not shown increases in strength, although this has been demonstrated in GH-treated children born small for gestational age and in those with Prader-Willi syndrome [20].

Individuals with GHD have adverse changes in lipids, and adults with GHD are at increased risk for adverse cardiovascular outcomes. Dyslipidemia is seen in children with GHD [28]. Improvement in serum concentrations of total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides has been shown after institution of GH therapy in GH deficient children and adolescents [29]. Other markers of increased cardiometabolic risk, including carotid artery intima media thickness and homocysteine levels, are also improved in GH deficient children following treatment [29, 30]. Unfortunately, regarding GH deficient children with spina bifida, there are no data regarding the effects of GH treatment on bone density, fracture risk, muscle mass and strength, and cardiometabolic risk.

Growth hormone treatment does lead to short term increases in height velocity in GH deficient children with spina bifida. Nearly all of the reports in the literature only examined treatment durations of a few years, and nearly all are retrospective. Two publications from large post-marketing surveillance databases reporting results from 80 and 81 children showed increases in height standard deviation score (SDS) from −2.97 to −2.01 and from −4.0 to −2.2 over the courses of 3 and up to 4 years, respectively [9, 31]. However, these databases rely on individual practitioners to report data collected without protocol and are prone to a number of biases. Additionally, the accuracy of height measurements is unclear. Rotenstein et al. reported an increase in the length SDS of 22 children with spina bifida and documented an increase from −2.5 to −1.9 [32]. The median duration of treatment was 2.83 years. In the only study reporting near adult height, a retrospective analysis of 20 children with spina bifida and GHD indicated that GH treatment led to an increase of the length SDS from −2.6 to −1.4 [33]. Most studies have evaluated the treatment response only in children with GHD. Some studies have included GHD and non-GHD subjects, but the two groups have not been separately analyzed. One study [32] provided a partial analysis of both groups and did not identify a difference in growth response in patients with GHD vs. those with normal GH secretion.

Both children and adults with GHD have lower ratios of lean body mass to fat mass. Most of the literature regarding GH treatment in spina bifida shows decreases in body mass index (BMI) SDS with treatment, although again data are very limited. In one of the post-marketing surveillance databases of GH treatment of children with spina bifida, BMI SDS decreased from +0.24 to −0.03 [9], while in a small study of 7 patients with GHD and spina bifida, BMI SDS decreased from a mean of +0.3 to −0.38 [34]. These changes are consistent with those seen in prospective treatment studies of otherwise healthy children with GHD.

Recognized side effects of GH treatment in otherwise healthy children include benign intracranial hypertension and slipped capital femoral epiphysis. Of particular concern in those with spina bifida are new or progressive scoliosis with or without tethered cord, increased risk for ventriculoperitoneal shunt revision, and the potential for disproportionate body segment growth. Again, data from treatment studies in spina bifida are limited. In the study of 7 children with GHD over 3 years, 2/7 had tethered cord associated with neurological symptoms and increasing scoliosis [34]. In Rotenstein’s study of 22 children treated for a median of 2.83 years, 5 were diagnosed with tethered cord and 6 required shunt revision [32]. Surgical release of tethered cord appears to increase the rate of linear growth [35]. Scoliosis did not progress in the study analyzing near adult height [33]. Data regarding disproportionate body segment growth are mixed. Hochhaus et al. evaluated this prospectively during the first year of GH treatment by comparing the change in length SDS to the change in arm span SDS [8]. The rate of change in the SDS scores was similar and led to similar increases in SDS after one year (+1.2 SDS for length and +1.3 SDS for arm span). Conversely, the small study by Trollmann et al. showed a faster increase in arm span than length that resulted in a statistically significant change in arm span SDS from −2.98 to −1.75, while there was no statistical change in length SDS [34]. The effect of the spinal level of myelomeningocele was not evaluated.

There are many issues regarding growth and GH treatment in spina bifida that remain unresolved and
are ripe for future research. Information on lean body mass before and after GH treatment do not exist. In addition, long-term cardiometabolic outcomes have not been assessed. Further, there are no studies examining the effects of GH on quality of life in individuals with spina bifida. Ideally these issues should be evaluated in the setting of prospective trials. Most of the publications provide data on the GHD population. Given the paucity of information about the effects of GH in the non-GH deficient population, we do not recommend routine use of GH in patients with spina bifida in the absence of GHD.

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The Spina Bifida Association has already embarked on a systematic process for reviewing and updating the guidelines. Future guidelines updates will be made available as they are completed.

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Conflict of interest

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References

[1] Duval-Beaupère G, Kaci M, Lougovoy J, Capomi MF, Touzeau C. Growth of trunk and legs of children with myelomeningocele. Dev Med Child Neurol. 1987 Apr; 29(2): 225-31. doi: 10.1111/j.1469-8749.1987.tb02140.x.
[2] Greene SA, Frank M, Zachmann M, Prader A. Growth and sexual development in children with meningomyelocele. Eur J Pediatr. 1985 Jul; 144(2): 146-8. doi: 10.1007/BF00451900.
[3] Löppönen T, Saukkonen AL, Serlo W, Tapanainen P, Ruokonen A, Knip M. Reduced levels of growth hormone, insulin-like growth factor-I and binding protein-3 in patients with shunted hydrocephalus. Arch Dis Child. 1997 Jul; 77(1): 32-7. doi: 10.1136/adc.77.1.32.
[4] Hochhaus F, Butenandt O, Schwarz HP, Ring-Mrozik E. Auxological and endocriniological evaluation of children with hydrocephalus and/or meningomyelocoele. 1997 Aug; 156(8): 597-601. doi: 10.1007/s004310050672.
[5] Trollmann R, Strehl E, Wenzel D, Dörr HG. Arm span, serum IGF-I and IGFBP-3 levels as screening parameters for the diagnosis of growth hormone deficiency in patients with myelomeningocele-preliminary data. Eur J Pediatr. 1998 Jun; 157(6): 451-5. doi: 10.1007/s004310050851.
[6] Perrone L, Del Gazzo D, D’Angelo E, Rea L, Di Manso G, Del Gado R. Endocrine studies in children with myelomeningocele. J Pediatr Endocrinol Metab. Jul-Sep 1994; 7(3): 219-23. doi: 10.1515/jpemd.1994.7.3.219.

[7] Apkon SD, Grady R, Hart S, Lee A, McNalley T, Niswander L, et al. Advances in the care of children with spina bifida. Adv Pediatr. 2014 Aug; 61(1): 33-74. doi: 10.1016/j.yapd.2014.03.007.

[8] Hochhaus F, Butenandt O, Ring-Mrozik E. One-year treatment with recombinant human growth hormone of children with meningomyelocele and growth hormone deficiency: A comparison of supine length and arm span. J Pediatr Endocrinol Metab. Mar-Apr 1999; 12(2): 153-9. doi: 10.1515/jpem.1999.12.2.153.

[9] Trollmann R, Bakker B, Lundberg M, Doerr HG. Growth in pre-pubertal children with myelomeningocele (MMC) on growth hormone (GH): The KGs experience. Pediatr Rehabil. Apr-Jun 2006; 9(2): 144-8. doi: 10.1080/136388050937465.

[10] O’Neill J, Fuqua JS. Short Stature and the Effect of Human Growth Hormone. Spina Bifida Association. Guidelines for the care of people with spina bifida 2018 [Available from: https://www.spinabifidaassociation.org/guidelines/.

[11] Dicianno BE, Beierwaltes P, Dosa N, Raman L, Chelliah J, Lanes R, Gunczler P, Lopez E, Esaa S, Villaroel O, Revel-Chion R. Cardiac mass and function, carotid artery intimamedia thickness, and lipoprotein levels in growth hormone-deficient adolescents. J Clin Endocrinol Metab. 2001 Mar; 86(3): 1061-5. doi: 10.1210/jcem.86.3.1061.

[12] Dunham RB. Nominal Group Technique: A Users’ Guide. Madison: Wisconsin School of Business; 1998.

[13] Harvey N, Holmes CA. Nominal group technique: An effective method for obtaining group consensus. Int J Nurs Pract. 2012 Apr; 18(2): 100816. doi: 10.1111/j.1099-1103.2010.00005.

[14] O’Connell MR. Drafting Agreement with the Single Text Approach 2012 [Available from: https://viaconflict.wordpress.com/2012/05/13/drafting-agreement-the-single-textapproach/.

[15] Van de Ven AH, Delbecq AL. The nominal group as a research instrument for exploratory health studies. Am J Public Health. 1972 Mar; 62(3): 337-42. doi: 10.2105/ajph.62.3.337.

[16] Hagan JF, Shaw JS, Duncan PM. Bright Futures: Guidelines for health supervision of infants, children, and adolescents. Chicago: American Academy of Pediatrics; 2007.

[17] Rotenstein D, Adams M, Reigel DH. Adult stature and anthropomorphic measurements of patients with myelomeningocele. 1995 May; 154(5): 398-402. doi: 10.1007/BF02072114.

[18] Gazzetti C, Ibaa A, Pila S, Beltrami N, Di Jorgi N, Rollo A, et al. Cut-off limits of the peak GH response to stimulation tests for the diagnosis of GH deficiency in children and adolescents: Study in patients with organic GHD. Eur J Endocrinol. 2016 Jul; 175(1): 41-7. doi: 10.1530/EJE-16-0105.

[19] Improda N, Capalbo D, Esposito A, Salermo M. Muscle and skeletal health in children and adolescents with GH deficiency. Best Pract Res Clin Endocrinol Metab. 2016 Dec; 30(6): 771-783. doi: 10.1016/j.ebel.2016.11.012.

[20] Saggese G, Baroncelli GI, Bertelloni S, Barsanti S. J Clin endocrinol metab the effect of long-term growth hormone (GH) treatment on bone mineral density in children with GH deficiency. Role of GH in the Attainment of Peak Bone Mass. 1996 Aug; 81(8): 3077-83. doi: 10.1210/clinex.81.8.8768878.

[21] Underwood LE, Attie KM, Baptista J, Genentech Collaborative Study Group. Growth hormone (GH) dose-response in young adults with childhood-onset GH deficiency: A two-year, multicenter, multiple-dose, placebo-controlled study. J Clin Endocrinol Metab. 2003 Nov; 88(11): 5273-80. doi: 10.1210/jc.2003-030204.

[22] Holmer H, Svensson J, Rylander L, Johannsson G, Rosén T, Bengtsson BA, et al. Fracture incidence in GH-deficient patients on complete hormone replacement including GH. J Bone Miner Res. 2007 Dec; 22(12): 1842-50. doi: 10.1359/jbmr.070811.

[23] Mo D, Fleseriu M, Qi R, Jia N, Child CJ, Bouillon R, et al. Fracture risk in adult patients treated with growth hormone replacement therapy for growth hormone deficiency: A prospective observational cohort study. Lancet Diabetes Endocrinol. 2015 May; 3(5): 331-8. doi: 10.1016/S2213-8587(15)00098-4.

[24] Högler W, Shaw N. Childhood growth hormone deficiency, bone density, structures and fractures: Scrutinizing the evidence. Clin Endocrinol (Oxf). 2010 Mar; 72(3): 281-9. doi: 10.1111/j.1365-2265.2009.03686.x.

[25] Baronecci GI, Bertelloni S, Sodini F, Saggese G. Lumbar bone mineral density at final height and prevalence of fractures in treated children with GH deficiency. J Clin Endocrinol Metab. 2002 Aug; 87(8): 3624-31. doi: 10.1210/jcem.87.8.8754.

[26] Schweizer R, Martin DD, Haase M, Roth J, Trebar B, Binder G, et al. Similar effects of long-term exogenous growth hormone (GH) on bone and muscle parameters: A pQCT study of GH-deficient and small-for-gestational-age (SGA) children. Bone. 2007 Nov; 41(5): 875-81. doi: 10.1016/j.bone.2007.06.028.

[27] Lanès R, Gunczler P, Lopez E, Esaa S, Villaroel O, Revel-Chion R. Cardiac mass and function, carotid artery intimamedia thickness, and lipoprotein levels in growth hormone-deficient adolescents. J Clin Endocrinol Metab. 2001 Mar; 86(3): 1061-5. doi: 10.1210/jcem.86.3.1061.

[28] Baronecci GI, Bertelloni S, Sodini F, Saggese G. Lumbar bone mineral density at final height and prevalence of fractures in treated children with GH deficiency. J Clin Endocrinol Metab. 2002 Aug; 87(8): 3624-31. doi: 10.1210/jcem.87.8.8754.

[29] Chen M, Gan D, Luo Y, Rampersad S, Xu L, Yang S, et al. Effect of recombinant human growth hormone therapy on blood lipid and carotid intimamedia thickness in children with growth hormone deficiency. Pediatr Res. 2018 May; 83(5): 954-960. doi: 10.1038/pr.2017.271.

[30] Calabro D, Mattace Raso G, Esposito A, Di Mase R, Barbieri F, Meli R, et al. Cluster of cardiometabolic risk factors in children with GH deficiency: A prospective, case-control study. Clin Endocrinol (Oxf). 2014 Jun; 80(6): 856-62. doi: 10.1111/cen.12393.

[31] Rotenstein D, Breem TJ. Growth hormone treatment of children with myelomeningocele. J Pediatr. 1996 May; 128(5 Pt 2): S28-31. doi: 10.1016/0022-3476(96)00007-0.

[32] Rotenstein D, Reigel DH. Growth hormone treatment of children with neural tube defects: Results from 6 months to 6 years. J Pediatr. 1996 Feb; 128(2): 184-9. doi: 10.1016/0022-3476(96)00387-6.

[33] Rotenstein D, Bass AN. Treatment to near adult stature of patients with myelomeningocele with recombinant human growth hormone. J Pediatr Endocrinol Metab. 2004 Sep; 17(9): 1195-200. doi: 10.1515/jpem.2004.17.9.1195.

[34] Trollmann R, Strehl E, Wenzel D, Dörr HG. Does growth hormone (GH) enhance growth in GH-deficient children with myelomeningocele? J Clin Endocrinol Metab. 2000 Aug; 85(8): 2740-3. doi: 10.1210/jcem.85.8.6724.

[35] Rotenstein D, Reigel DH, Lucke JF. Growth of growth hormone-treated and nontreated children before and after tethered spinal cord release. Pediatr Neurosurg. 1996; 24(5): 237-41. doi: 10.1159/000121045.