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Puberty, statural growth, and growth hormone release in children with cerebral palsy

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Abstract

Objective—Children with cerebral palsy (CP) are smaller than normally growing children.. The association between the growth hormone (GH) axis and growth in children with CP during puberty is unknown. We compared growth and markers of the GH axis in pre-pubertal and pubertal children with moderate to severe CP and without CP over a three-year period.

Study design—Twenty children with CP, ages 6–18, Gross Motor Function Classification System levels III–V, were compared to a group of sixty-three normally growing children of similar age. Anthropometry, Tanner stage, bone age, and laboratory analyses were performed every six months for three years. Laboratory values included spontaneous overnight GH release, fasting IGF-1 and IGFBP-3. Repeated measures models were used to evaluate interactions among Tanner stage and group (children with CP vs. reference children), taking into account gender, age, and nutritional status.

Results—Children with CP grew more slowly than those without CP at all Tanner stages ($p < 0.01$). Patterns of IGF-1 and GH secretion in children with CP were similar to those of the reference group; however, the concentrations of IGF-1 ($p < 0.01$) and GH ($p < 0.01$) were lower in girls with CP, with a similar trend for boys ($p = 0.10$ and 0.14 , respectively).

Conclusions—Diminished circulating IGF-1 and GH concentrations may explain the differences in growth between the two groups.

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There are no conflicts of interest.

Keywords

cerebral palsy; growth; growth hormone; stature

1. INTRODUCTION

According to definition, “cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy, and by secondary musculoskeletal problems”[1]. Although the primary impairment in CP is in motor function, abnormal growth is common in children and adolescents with CP[2,3].

Abnormalities in growth, once thought to be intrinsic to CP, result from a variety of causes. Malnutrition (predominantly protein calorie malnutrition) [4,5], endocrine dysfunction[6,7], and a variety of other factors, such as mechanical forces and neurological differences[7,8] contribute to slow growth. All of these appear to act synergistically, resulting in slow statural growth and weight gain.

Growth during puberty involves a complex interplay of many factors, including hormones (especially sex and growth hormones), genetics, and environment[9,10]. The differences in growth between children with and without CP increase with age[4] and the typical pubertal growth spurt appears to be significantly diminished in children with CP[2,3]. At puberty, normal children undergo a growth spurt with an increase in height velocity from 5–6 centimeters per year to 9–10 centimeters per year at peak (usually at mid-puberty). Descriptive growth curves taken from cross sectional data of children with CP show a fairly steady height velocity before and during puberty[2,3]. This divergence from normal growth is suggestive of an endocrinopathy[4].

Previous studies have demonstrated GH deficiency in some children with CP [6,11,12]. Based on this, we hypothesized that diminished growth in children with CP is associated with dysfunction of the hypothalamic-pituitary axis. To test this hypothesis, we measured statural growth and circulating concentrations of growth hormone (GH), insulin-like growth factor I (IGF-1), and insulin-like growth factor binding protein-3 (IGFBP-3) in pre-pubertal and pubertal children with CP and compared them to the same measures in normally growing pre-pubertal and pubertal children.

Studying discrepant growth rates between children with CP and normally growing children is necessary given recent evidence that suggests that diminished growth in children with CP is associated with increased health care utilization and decreased social participation[2,13]; thus, understanding the growth pattern in this population is important to children, caregivers, and society. This study examined only one of the myriad factors associated with diminished growth in children with CP: abnormality of the GH-IGF-1 axis.

2. METHODS

This study was designed as a sub-study of the North American Growth in Cerebral Palsy Project (NAGCPP) [14]. Anthropometry, pubertal staging (Tanner), and laboratory studies of the GH axis were performed at baseline and every 6 months. Skeletal ages were obtained at baseline and every 12 months thereafter. The reference study was ongoing for 5 years and data (minimum of three-year follow-up) were available for 63 subjects who were part of a

longitudinal study of the endocrine control of growth, maturation and body composition at the University of Virginia General Clinical Research Center (methods published previously)[15].

A. Inclusion/Exclusion criteria

Children with moderate-to-severe CP, ages 6–18, who were participants in the NAGCPP study were eligible for inclusion in the study. Children with a history of genetic, metabolic, or neuro-degenerative disease, or children with medical conditions affecting growth were excluded.

B. Participants

Twenty children with moderate-to-severe CP, ages 6–18, with Gross Motor Function Classification System (GMFCS) level III–V, were enrolled in the study, and compared to a reference group of 63 normally growing children. The study was approved by the University of Virginia Institutional Review Board. Informed consent was obtained from the child's parent or legal guardian and assent was obtained from the child when possible.

C. Anthropometry

Anthropometry was performed using techniques described in [The Methods of Auxological Anthropometry](#)[16]. Two averaged measurements of weight, triceps skinfold, and knee height were obtained in all participants with CP; measurements were the same for normally growing children, but included stature rather than knee height. Knee height, measured with knee height calipers (Ross labs, Columbus, Ohio), was used to estimate height in children with CP using published formulas [17]. Skinfold measurements were taken with Harpenden calipers (Baty International, United Kingdom). Research staff responsible for obtaining anthropometric measures for the NAGCPP study trained together and against a reference anthropometrist (W. Cameron Chumlea, Fels Institute).

D. Measures of maturation

Development of secondary sex characteristics (breasts in girls; pubic hair in boys) was assessed by a developmental pediatrician or the research coordinator using the methods of Tanner[18]. Observers were trained in the assessment of sexual maturation by one of the principal investigators of the American Academy of Pediatrics, Pediatric Research in Office Settings (AAP PROS) network study of sexual maturation in girls. Details of the training are published elsewhere[19,20]. Left hand and wrist radiographs were obtained to assess skeletal maturation. These were interpreted for skeletal maturity by a developmental pediatrician (CMH) formally trained in the Fels method[21].

E. Clinical Assessment and Measurement of Functional Impairment

Participants were assessed by a developmental pediatrician for type of CP and for functional motor impairment using the GMFCS. The GMFCS is a method of classifying motor involvement of children with CP based on their mobility either independently or with assistive devices such as walkers or wheelchairs. This is a reliable and valid method of communicating motor function for both research and clinical purposes. Levels range from I to V with individuals at level V having the greatest motor impairment. Children with moderate to severe CP enrolled in this study were levels III–V [22].

F. Laboratory Assays

Spontaneous overnight GH concentrations (sampled every 20 minutes for 12 hours) were measured using the Nichols chemiluminescent assay (Nichols Institute Diagnostics, San Clemente, CA, intra-assay coefficient of variation 6%, inter-assay coefficient of variation 7.2%). Intraindividual measurements of spontaneous growth hormone (separated in time) have

been shown in the past to be well correlated[23]. Samples for IGF-1 were obtained while fasting and concentrations were measured using the Nichols Radioimmunoassay (intra-assay coefficient of variation 4.5%, inter-assay coefficient of variation 9.7%) (Nichols Institute Diagnostics, San Clemente, CA). Samples for IGFBP-3 were obtained while fasting and were measured using DSL IRMA (Diagnostic Systems Laboratories, Webster, TX; intra-assay coefficient of variation 2.4%, inter-assay coefficient of variation 1.9%).

G. Statistical Analysis

Repeated measures models were fit to compare children with CP to the normally developing children for the following outcomes within each Tanner stage: change in height and weight, and concentrations of GH, IGF-1, and IGFBP-3. For ease of interpretation, and due to a disparate number of observations at certain Tanner stages between males and females, the models were fit separately for each gender. The models were fit to the data using restricted maximum likelihood estimation (REML)[24]. Overall *F*-tests assessed the significance of the model variables of interest, namely: group, Tanner stage, and their interaction, adjusting for age. A significant interaction between Tanner stage and group (CP or not) would indicate that the mean change in the outcome across the spectrum of Tanner stages differs between the groups. If an interaction were not significant, then one would expect to see parallel trends over Tanner stage for the two groups. In the case where a similar pattern across Tanner stages was observed, we then assessed for an overall difference in hormone level (the “group” effect”), essentially a measure of the constant difference between the parallel lines. To account for potential discrepancies in nutritional adequacy, all models also included baseline triceps skinfold z-scores for each child, as calculated using reference values from Frisancho [25]. The Kenward-Roger approximation of the degrees of freedom was used to compute p-values from the overall tests[26]. A first-order autoregressive correlation structure between measurements on the same individual was assumed. The models used all the available data on participants, including those who dropped out of the study or had intermittently missing data. Due to the limited number of observations in certain Tanner stages, we only modeled the outcomes of interest across the first four Tanner stages for girls and across the first two Tanner stages for boys (during the time-frame of the study, the children in the CP group did not progress beyond these Tanner stages). Given the relatively small number of subjects, the exploratory nature of this study, and the characteristics of the models utilized, we chose to specify our level of significance as $\alpha=0.01$ for all results in order to minimize the chance of a Type I error.

3. RESULTS

A. Descriptive statistics

Table 1 shows baseline demographics of the children with CP and the reference children. Variables include baseline gender, race/ethnicity, Tanner stage, GMFCS, age, bone age, and Z-scores for height, weight, and triceps skinfold. Race and ethnic distribution were similar in the two groups. Tanner stage distribution was not significantly different between children with CP and reference children (Wilcoxon p-value = 0.61). Baseline triceps skinfolds, height, weight, and BMI Z-scores were lower in the group of children with CP (t-test p-values < 0.05).

Table 2 describes the number of total observations at each Tanner stage (breasts for girls, pubic hair for boys) for each of the primary outcome variables in both groups of children. Variables include change in height, IGF-1, GH, and IGF-BP3 concentrations. Very few of the boys with CP progressed beyond Tanner stage II. Of the 20 children with CP, 19 completed the study. One participant died before the study was complete due to an unrelated cause.

B. Skeletal Age

Since bone ages were available only at yearly visits, bone age was not accounted for in the primary longitudinal analysis. However, differences were observed in baseline bone age and chronological age between children with and without CP. On average, baseline bone age was almost 10 months (0.80 years) behind chronological age in children with CP. Conversely, baseline bone age was about 5 months (0.41 years) ahead of chronological age in the reference group. The difference in the groups with respect to age discrepancy was significant (t-test p-value < 0.001).

C. Statural Growth

Children with CP differed from the reference subjects in model-predicted height velocity across Tanner stages. Models of annual change in height for girls showed that the height velocity of girls with CP across Tanner stages was overall lower than that of the reference girls ($p = 0.0024$). The same result was found in boys ($p = 0.0070$). There was no significant difference in the pattern of height velocity across the pubertal stages (i.e., no significant interaction between group and Tanner stage) for either boys or girls. Figure 1a displays the predicted annual statural growth at each Tanner stage for both girls and boys (CP and reference groups), after adjusting for age and baseline triceps Z-score (mean age and baseline triceps Z-score for the entire dataset were used in these figures),

D. Weight change

Similar models of annual change in weight were fit, and similar results to those of statural growth were observed. Children with CP gained less weight overall than those without CP ($p = 0.0007$ for girls and 0.0311 for boys).

E. Growth hormone

The pattern of GH release across Tanner stages was similar for children with and without CP. However, GH release was lower overall for those with CP. This difference was significant for girls ($p = 0.0099$), with a trend towards significance for boys ($p = 0.0972$). Figure 1b displays model-predicted GH AUC values for both groups and genders after adjusting for age and baseline triceps z-score.

F. IGF-1

The pattern of IGF-1 concentrations in children in the CP group was similar to that in the reference group. However, the overall concentration of IGF-1 was lower in girls with CP ($p = 0.0002$) than in girls in the reference group. IGF-1 was also lower in boys with CP than in the reference group although the difference between the two groups was not statistically significant ($p = 0.1424$). Figure 1c displays the model-predicted levels of IGF-1 across Tanner stages.

G. IGFBP-3

As exhibited in Figure 1d, the pattern of IGFBP-3 concentration was somewhat different when comparing girls with and without CP ($p = 0.0158$). There was no statistically significant difference in IGFBP-3 concentration or pattern across Tanner stages for boys.

4. DISCUSSION

Prior studies have shown that some children with CP have decreased GH secretion both spontaneously, and with provocation[6,12]. This is the first longitudinal study to show that children with CP had diminished GH concentration compared to that of the reference group as well as lower circulating concentrations of IGF-1.

Results of this study support previous findings that height velocity in children with CP is decreased compared to that in normally growing children[27]; further, this is the first longitudinal study to demonstrate diminished height velocity in prepubertal and pubertal children with CP. In addition, this study offers new evidence that IGF-1 and GH concentrations are diminished in the group of girls with CP compared with reference group; given that IGF-1 concentrations are correlated with statural growth[28], this is an important observation. While it is not certain that diminished IGF-1 directly causes the diminished statural growth observed in this study, we do know that the two are associated. Unfortunately, due to the size of the study, it was impossible to directly assess the impact of IGF-1 levels on statural growth.

The cause of low IGF-1 concentration in the group of girls with CP is unclear. Malnutrition, common in children with CP and known to cause of low IGF-1, must be considered in interpreting the low concentrations of IGF-1 in this study. In a properly functioning GH axis, circulating IGF-1 provides feedback to the hypothalamus and pituitary which influence levels of GH secretion. A low concentration of IGF-1 (typically accompanied by a low IGFBP-3 concentration) should lead to increased GH secretion, as is seen in severely malnourished children[29]. The combination of low IGF-1 and GH found in this study suggest that malnutrition is not responsible for the low IGF-1 concentration. In this case, the low concentration of GH secretion in the girls with CP may reflect an under-functioning of the hypothalamic-pituitary axis and could be considered a form of partial growth hormone deficiency. Furthermore, low concentrations of IGF-1 and growth hormone were noted even when controlling for malnutrition by including a measure of nutritional status, triceps skinfold Z-score, in the statistical model. Triceps skinfold Z-score was selected as a measure of nutritional status rather than BMI or weight-for-height because it correlates better than other single measures of nutritional status in individuals with CP [30].

Limitations of this study include factors related to participant enrollment, measurement and interpretation bias, and laboratory challenges which arose throughout the project. Considering that CP is a heterogeneous diagnosis based on description of physical findings rather than etiology, the small sample size and limited diversity (in ethnicity, CP type, and functional status) limit how well these findings can be generalized to all children with CP.

Our intention was to document growth and hormonal concentrations in a group of children with CP as they progressed through puberty, but this proved difficult to accomplish, particularly in the boys. There were not large enough numbers of male participants who progressed through puberty during the course of the study to analyze data on boys beyond Tanner stages I and II (table 1). The relatively small number of boys in this study may be the reason statistical significance was not achieved for many of the model results. Thus, no definitive conclusions about gender differences in this examination of children with CP can be made.

We chose to use pubic hair as a marker of puberty in boys rather than genital development because, based on visual inspection, it is difficult to accurately differentiate genital size in males. Although this introduces the possibility that we might mislabel as pubertal a number of truly prepubertal boys due to premature adrenarche, this seemed the best way to achieve consistency in Tanner staging of male participants. Since few boys in the study progressed beyond Tanner stage II, it seems unlikely that premature adrenarche in boys has skewed our findings. The potential for bias was also present in interpretation of skeletal ages given that one observer (formally trained in the Fels method) interpreted all skeletal ages for the group with CP. The same methodology was employed in the reference group, but interpretation was by a different trained observer.

Another limitation is the difference between techniques used to measure statural growth in the group of children with CP and the reference group: namely, the use of knee height (converted

to stature) for participants with CP and the use of stature for participants without CP. Reliable measures of height or length in children with CP are often impossible to obtain due to fixed joint contractures, involuntary muscle spasms, and poor cooperation due to associated cognitive deficits [31,32]. Segmental measures such as knee height, have been investigated for use as alternatives to length or stature in children with CP [31] and have been recommended for children and adults with various disabilities because of their documented reliability[33]. Formulas for estimating stature from knee height have been developed for children with cerebral palsy [17,34]. Because segmental measures are reliable they may offer a better estimate of stature in children with moderate to severe CP than recumbent length; thus, we chose to compare knee height (converted to stature) in participants with CP to stature in participants without CP.

Another limitation arises from our use of norms for triceps skinfold measure created by Frisancho[25]; these were based on a cross sectional observational study performed in the 1970's and were not based on measurements of individuals with CP; thus, it is difficult to be certain how well they apply to this population.

A final limitation in statistical analysis of the data, was a change in laboratory assays for IGF-1 at the General Clinical Research Center during the study. All of the samples from the reference group were assayed using the Nichols RIA; however, samples from the group of children with CP were assayed in the early part of the study using the Nichols RIA and then the Immulite 2000 in the late part of the study. Since (unfortunately) no studies were performed to compare the Nichols assay with the Immulite assay for IGF-1, we chose the conservative approach of limiting our analysis to results obtained with the Nichols assay only. This approach diminishes statistical power, but eliminates any potential bias in treating values from the two assays as equivalent.

Despite limitations, this study does offer valuable insight into the GH-IGF-1 axis in pre-pubertal and pubertal children with CP. Differences in IGF-1 levels may explain differences in growth as well as bone age. Abnormalities in IGF-1 and GH concentrations suggest possible targets for intervention. Since IGF-1 is the main anabolic mediator of GH action, many of the functions of GH (bone mineral homeostasis, body composition, stature, and cognitive function) may be compromised when IGF-1 concentrations are diminished[28,35,36]. If raising IGF-1 concentrations with the use of GH or IGF-1 therapy could help children with CP grow taller, this could impact health. GH has been used with success to increase growth in children with idiopathic short stature, chronic illnesses or developmental disabilities (i.e. Turner syndrome, Prader-Willi Syndrome) even in the absence of GH deficiency. In children with cystic fibrosis, nutritional supplementation together with GH increased growth and decreased hospitalizations over nutritional supplementation alone[37]. Further, GH has been shown to increase growth and bone mineral density in children with CP[38]. We speculate that increasing growth in children with CP might lead to improvement in general health. This is, indeed, speculation and would require systematic evaluation by way of a prospective study. Further, this may be controversial given that developmentally disabled children (particularly those at GMFCS IV and V) may be easier to care for when they are small in size[39]. This issue warrants further investigation as the benefit of improved health may offset the potential increase in caregiver burden.

Clinical assessment and management of growth in children with CP should focus on all the factors that may affect a child's growth and health. Treatment of malnutrition, increasing weight bearing and a variety of other interventions may have measurable positive effects on growth in children with CP and merit further study. For example weight bearing is thought to increase bone density in non-ambulatory children with CP [40] but there has been no investigation of its effects on bone length. Abnormalities of the GH-IGF-1 axis are a small

piece of a complicated puzzle. At the least, the results of this study should increase awareness that the GH-IGF-1 axis may be abnormal in some children with CP. Physicians caring for these patients should consider investigating the GH axis when a child with CP has growth failure.

In summary, children with CP had diminished height velocity, IGF-1, and GH concentrations compared with the reference group. The lower IGF-1 and GH concentrations and statural growth may be linked. Further studies are needed to determine if increasing GH and IGF-1 concentrations might lead to increased growth in children with CP along with improved health and well being.

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References

1. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: The definition and classification of cerebral palsy, april 2006. *Developmental Medicine & Child Neurology* - Supplementum 2007 Feb;109:8–14.
2. Stevenson RD, Conaway M, Chumlea WC, Rosenbaum P, Fung EB, Henderson RC, et al. Growth and health in children with moderate-to-severe cerebral palsy. *Pediatrics* 2006;118(3):1010–1018. [PubMed: 16950992]
3. Day S, Strauss D, Vachon P, Rosenbloom L, Shavelle R, Wu Y. Growth patterns in a population of children and adolescents with cerebral palsy. *Developmental Medicine & Child Neurology* 2007;49:167. Available from: <http://www.lifeexpectancy.com/articles.shtml>. [PubMed: 17355471]
4. Stevenson RD, Hayes RP, Cater LV, Blackman JA. Clinical correlates of linear growth in children with cerebral palsy. *Developmental Medicine & Child Neurology* 1994;36(2):135–142. [PubMed: 8132124]
5. Stallings VA, Charney EB, Davies JC, Cronk CE. Nutrition-related growth failure of children with quadriplegic cerebral palsy. *Developmental Medicine & Child Neurology* 1993;35(2):126–138. 1993. [PubMed: 8444326]
6. Coniglio SJ, Stevenson RD, Rogol AD. Apparent growth hormone deficiency in children with cerebral palsy. 1996;38(9):797–804.
7. Stevenson RD, Roberts CD, Vogtle L. The effects of non-nutritional factors on growth in cerebral palsy. *Developmental Medicine & Child Neurology* 1995 Feb;37(2):124–130. [PubMed: 7851668]
8. Henderson RC, Grossberg RI, Matuszewski J, Menon N, Johnson J, Kecskemethy HH, et al. Growth and nutritional status in residential center versus home-living children and adolescents with quadriplegic cerebral palsy. *J Pediatr* 2007 Aug;151(2):161–166. [PubMed: 17643769]
9. Tanner JM, Whitehouse RH, Hughes PC, Carter BS. Relative importance of growth hormone and sex steroids for the growth at puberty of trunk length, limb length, and muscle width in growth hormone-deficient children. *Journal of Pediatrics* 1976 Dec;89(6):1000–1008. [PubMed: 993900]
10. Rogol AD, Roemmich JN, Clark PA. Growth at puberty. *Journal of Adolescent Health* 2002;31:192–200. [PubMed: 12470915]

11. Coniglio SJ, Stevenson RD. Growth hormone deficiency in two children with cerebral palsy. *Developmental Medicine & Child Neurology* 1995 Nov;37(11):1013–1015. [PubMed: 8566448]
12. Shim ML, Moshang T Jr, Oppenheim WL, Cohen P. Is treatment with growth hormone effective in children with cerebral palsy? *Dev Med Child Neurol* 2004 Aug;46(8):569–571. [PubMed: 15287249]
13. Samson-Fang L, Fung E, Stallings VA, Conaway M, Worley G, Rosenbaum P, et al. Relationship of nutritional status to health and societal participation in children with cerebral palsy. *J Pediatr* 2002 Nov;141(5):637–643. [PubMed: 12410191]
14. Liptak GS, O'Donnell M, Conaway M, Chumlea WC, Wolrey G, Henderson RC, et al. Health status of children with moderate to severe cerebral palsy. *Developmental Medicine & Child Neurology* 2001 Jun;43(6):364–370. [PubMed: 11409824]
15. Roemmich JN, Clark PA, Mai V, Berr SS, Weltman A, Veldhuis JD, et al. Alterations in growth and body composition during puberty: III. influence of maturation, gender, body composition, fat distribution, aerobic fitness, and energy expenditure on nocturnal growth hormone release. *Journal of Clinical Endocrinology & Metabolism* 1998 May;83(5):1440–1447. [PubMed: 9589636]
16. Cameron, N. The methods of auxological anthropology. Falkner, F.; Tanner, JM., editors. New York: Plenum Press; 1986.
17. Stevenson RD. Use of segmental measures to estimate stature in children with cerebral palsy. *Archives of Pediatrics & Adolescent Medicine* 1995;149(6):658–662. [PubMed: 7767422]
18. Tanner, JM. Growth at adolescence. 2nd Revised ed.. London, England: Blackwell Science Ltd.; 1978.
19. Worley G, Houlihan CM, Herman-Giddens ME, O'Donnell ME, Conaway M, Stallings VA, et al. Secondary sexual characteristics in children with cerebral palsy and moderate to severe motor impairment: A cross-sectional survey. *Pediatrics* 2002 Nov;110(5):897–902. [PubMed: 12415027]
20. Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, et al. Secondary sexual characteristics and menses in young girls seen in office practice: A study from the pediatric research in office settings network. *Pediatrics* 1997;99(4):505–512. [PubMed: 9093289]
21. Roche, AF.; Chumlea, WC.; Thissen, D. Assessing the skeletal maturity of the hand-wrist: Fels method. Springfield: Charles C. Thomas; 1988.
22. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Developmental medicine and child neurology* 1997;39:214–223. [PubMed: 9183258]
23. Ropelato MG, Martinez A, Heinrich JJ, Bergada C. Reproducibility and comparison of growth hormone secretion tests. *J Pediatr Endocrinol* 1996 Jan–Feb;9(1):41–50.
24. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics* 1982 Dec;38(4):963–974. [PubMed: 7168798]
25. Frisancho RA. New norms of upper limb fat and muscle areas for assessment of nutritional status. *Am J Clin Nutr* 1981;34:2540–2545. 1981. [PubMed: 6975564]
26. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics* 1997 Sep;53(3):983–997. [PubMed: 9333350]
27. Samson-Fang L, Stevenson RD. Linear growth velocity in children with cerebral palsy. *Developmental Medicine & Child Neurology* 1998 Oct;40(10):689–692. [PubMed: 9851238]
28. Laron Z. The essential role of IGF-I: Lessons from the long-term study and treatment of children and adults with laron syndrome. *Journal of Clinical Endocrinology & Metabolism* 1999 Dec;84(12):4397–4404. [PubMed: 10599694]
29. Soliman AT, Hassan AE, Aref MK, Hintz RL, Rosenfeld RG, Rogol AD. Serum insulin-like growth factors I and II concentrations and growth hormone and insulin responses to arginine infusion in children with protein-energy malnutrition before and after nutritional rehabilitation. *Pediatr Res* 1986 Nov;20(11):1122–1130. [PubMed: 3099250]
30. Samson-Fang LJ, Stevenson RD. Identification of malnutrition in children with cerebral palsy: Poor performance of weight-for-height centiles. *Developmental Medicine & Child Neurology* 2000 Mar;42(3):162–168. [PubMed: 10755455]
31. Spender QW, Cronk CE, Charney EB, Stallings VA. Assessment of linear growth of children in cerebral palsy: Use of alternative measures to height or length. *Dev Med Child Neurol* 1989;31:206–214. 1989. [PubMed: 2737373]

32. Tobis JS, Saturen P, Larios G, Posniak AO. Study of growth patterns in cerebral palsy. *Arch Phys Med Rehabil* 1961;42:475–481. 1961. [PubMed: 13777130]
33. Stevenson RD. Measurement of growth in children with developmental disabilities. *Developmental Medicine & Child Neurology* 1996;38(9):855–860. [PubMed: 8810718]
34. Chumlea WC, Guo SS, Steinbaugh ML. Prediction of stature from knee height for black and white adults and children with application to mobility-impaired or handicapped persons. *J Am Diet Assoc* 1994;94:1385–1388. 1994. [PubMed: 7963188]
35. Laron, Z. Growth hormone and insulin-like growth factor-I: Effects on the brain. In: Pfaff, DW.; Arnold, AP.; Etgen, AM.; Fahrbach, SE.; Rubin, RT., editors. *Hormones, Brain and Behavior*. San Diego/Amsterdam: Academic Press/Elsevier Science; 2002. p. 75
36. Laron Z. Childhood-onset growth hormone deficiency, cognitive function and brain N-acetylaspartate. *Psychoneuroendocrinology* 2006 Jun;31(5):680. [PubMed: 16488083]
37. Hardin DS, Stratton R, Kramer JC, Reyes de la, Rocha S, Govaerts K, Wilson DP. Growth hormone improves weight velocity and height velocity in prepubertal children with cystic fibrosis. *Hormone & Metabolic Research* 1998;30(10):636–641. [PubMed: 9851673]
38. Ali O, Shim M, Fowler E, Greenberg M, Oppenheim W, Cohen P. Growth hormone therapy improves bone mineral density in children with cerebral palsy: A preliminary pilot study. *The Journal of Clinical Endocrinology & Metabolism* 2007;92(3):932. [PubMed: 17179200]
39. Gunther DF, Diekema DS. Attenuating growth in children with profound developmental disability: A new approach to an old dilemma. *Archives of Pediatrics & Adolescent Medicine* 2006 Oct;160(10):1013–1017. [PubMed: 17018459]
40. Caulton JM, Ward KA, Alsop CW, Dunn G, Adams JE, Mughal MZ. A randomised controlled trial of standing programme on bone mineral density in non-ambulant children with cerebral palsy. *Archives of Disease in Childhood* 2004 Feb;89(2):131–135. [PubMed: 14736627]

Girls

Boys

Girls

Boys

Girls

Boys

Figure 1.

Figure 1a: Model Predicted* Yearly Change in Height in Children with CP compared to Typically Growing Children

Figure 1b: Model Predicted* Growth Hormone Area Under the Curve Values in Children with CP compared to Typically Growing Children

Figure 1c: Model Predicted* IGF-1 Values in Children with CP compared to Typically Growing Children

Figure 1d: Model Predicted* IGFBP-3 Values in Children with CP compared to Typically Growing Children

*Adjusting for age and baseline triceps z-score (predicted values using the mean age and triceps z-score the entire group of girls and boys, respectively)

Table 1

Baseline Demographics: Children with CP and Typically growing Children

Characteristic	Children with CP (n = 20)	Typically growing Children (n = 63)
Number of Children (% in Group)		
Male	9 (45%)	33 (53%)
Race/Ethnicity		
Caucasian	17 (85%)	55 (84%)
African American	1 (5%)	5 (8%)
Other	2 (10%)	5 (8%)
Tanner Stage *		
I	9 (45%)	34 (54%)
II	4 (20%)	6 (10%)
III	2 (10%)	11 (17%)
IV	5 (25%)	11 (17%)
V	0 (0%)	1 (2%)
GMFCS		
3	2 (10%)	--
4	4 (20%)	--
5	14 (70%)	--
Mean (SD)		
Age	10.1 (2.7)	11.6 (1.7)
Bone Age	9.3 (2.8)	12.0 (1.9)
Triceps Z-score	-0.5 (1.1)	0.4 (0.9)
Height Z-score	-3.6 (1.5)	0.2 (1.0)
Weight Z-score	-3.2 (2.6)	0.2 (1.0)
BMI Z-score	-0.6 (1.6)	0.2 (0.9)

* Defined by pubic hair for boys; breasts for girls

Table 2

Number of Total Observations at each Tanner Stage (by Gender and Group)

Variable	Tanner Stage									
	Children with CP					Typically growing Children				
	I	II	III	IV	V	I	II	III	IV	V
<i>Girls</i>										
Change in height (between two successive measurements)	5	6	9	21	4	27	16	22	50	74
IGF-I	4	7	6	16	1	39	19	30	56	75
GH	7	8	9	25	4	36	17	26	52	65
IGF-BP3	7	8	11	26	4	27	6	19	34	21
<i>Boys</i>										
Change in height (between two successive measurements)	19	14	4	1	0	51	32	23	49	47
IGF-I	17	9	2	0	0	73	35	26	54	47
GH	23	14	3	1	0	72	34	23	49	43
IGF-BP3	25	16	4	1	0	50	15	9	17	8

* Shaded areas highlight the very small number of observations at these Tanner stages for boys and girls, the reason why these Tanner stages were not included in the final models.