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Growth Hormone Deficiency in Children and Adolescents with Cerebral Palsy: Relation to Gross Motor Function and Degree of Spasticity

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Abstract: Children with Cerebral Palsy (CP) often have poor linear growth during childhood with short final height. Thus, we aimed to assess serum growth hormone (GH), insulin like growth factor-1 (IGF-1) and insulin like growth factor binding protein-3 (IGFBP-3) levels among CP patients and their relation to each of gross motor function and degree of spasticity. Fifty CP children and adolescents were studied in comparison to 50 healthy age-, sex- and pubertal stage-matched children and adolescents. All subjects were subjected to clinical evaluation, Intelligence Quotient (IQ) assessment and measurement of serum GH, IGF-1and IGFBP-3. All auxological and hormonal parameters were significantly lower among cases. Fifty two% of cases were GH-deficient and 62% had reduced IGF-1and IGFBP-3 levels. Gross Motor Function Measure- 88 (GMFM-88) score correlated negatively with each of basal ($r = -0.71$, $p = 0.02$) and peak stimulated GH ($r = -0.88$, $p = <0.001$); IGF-1 ($r = -0.64$, $p = 0.04$) and IGFBP-3 ($r = -0.69$, $p = 0.031$). There were significant negative correlations between the degree of spasticity assessed by Modified Ashworth Scale and each of basal ($r = -0.61$, $p = 0.032$) and peak stimulated GH ($r = -0.78$, $p = 0.01$); IGF-1 ($r = -0.65$, $p = 0.041$) and IGFBP-3 ($r = -0.62$, $p = 0.035$). Growth Hormone Deficiency (GHD) is prevalent in children with CP and could be one of the causes of their short stature.

Key words: Cerebral palsy, growth hormone deficiency, insulin like growth factor-1, insulin like growth factor binding protein-3, short stature

INTRODUCTION

CP is a static encephalopathy defined as a non progressive disorder of posture and movement resulting from a defect or lesion of the developing brain (Ziadat, 2007). It is a common disorder, with an estimated prevalence in the general population of 2/1000 (Cavlak and Kavlak, 2005). Major causes of CP involve prematurity, abnormal intrauterine development due to fetal-maternal infections, asphyxia during delivery, brain trauma during labor and delivery and complications in the perinatal period. Independent of causal factors responsible for the development of CP, the disease has a strong socioeconomic impact. Currently there is no cure for CP and the therapeutic approaches of physical therapy, occupational therapy, speech therapy, neuropsychology, pharmacology and surgery achieve only partial benefits for affected individuals (Krageloh-Mann and Cans, 2009).

Growth is an important biological process during childhood (Mohammadian and Khoddam, 2007). It has been shown that children with CP often have poor linear growth during childhood, resulting in a diminished final adult height, an issue that has received little attention so far (Kruse *et al*., 2009). Recently, some investigators demonstrated that children with CP show deficient GH secretion, by using provocative tests for GH and that their low IGF-1 and GH levels may explain their low height for age and short final height (Kruse *et al*., 2009; Kuperminc *et al*., 2009). However, the number of studies in which it has been reported whether or not GH secretion is impaired in CP is quite limited (Shim *et al*., 2004). Thus, a better understanding of the causes and mechanisms of growth impairment in CP is essential as it could lead to its prevention or treatment in some of those children (Shim *et al*., 2004). Given the complexity of GH neuroregulation (Nia and Salehi, 2008) it seems logical to postulate that severe brain damage may affect a number of neurotransmitter pathways involved in GH control, thus affecting the normal secretion of the hormone (Reimunde *et al*., 2010). Moreover, osteopenia is a common finding in children with CP and seems to be associating decreased IGF-1 and IGFBP3 plasma levels, the usual markers of deficient GH secretion (Ali *et al*., 2007). Other possible causes of decreased growth in CP include psychosocial deprivation and suboptimal

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nutritional status which are also involved in subnormal GH secretion (Coniglio *et al*., 1996). Thus, GH therapy could be beneficial in improving the growth velocity of GH-deficient CP children, thus improving their final height (Reimunde *et al*., 2010) especially that recombinant human GH is generally safe in treating children with short stature due to GHD or other causes (Chang and Hui, 2011).

With this background, we were stimulated to assess serum GH (basal and peak stimulated), IGF-1 and IGFBP-3 levels among CP patients and their relation to each of gross motor function and degree of spasticity.

MATERIALS AND METHODS

Study population: This cross sectional case-control study was conducted on 50 Egyptian children and adolescents with CP (29 males, 21 females) whose ages ranged between 3.2 and 11.5 years (mean age: 6.5±3.05 years). All patients were shorter than expected for their chronological age (height SDS <-2) (Cole, 2002). The etiology of CP was due to perinatal hypoxia in 23 patients (46%), prenatal asphyxia in 5 patients (10%), prematurity in 12 patients (24%), prenatal infections in 4 patients (8%), kernicterus in 4 patients (8%) and postnatal encephalitis in 2 patients (4%).

CP patients were studied in comparison to 50 healthy age-, sex- and pubertal stage-matched children and adolescents (28 males, 22 females) serving as controls. Their ages ranged between 3.6 and 11.4 years (mean age: 6.8±2.15 years). The latter were normally growing children having no clinical findings suggesting neither endocrine disorders nor neuropsychiatric manifestations.

None of the studied subjects were taking medications that might influence the GH-IGF-1 axis. Children with history of genetic, metabolic, or neurodegenerative diseases, or children with medical conditions affecting growth were excluded from the study.

All subjects were recruited from the Pediatric Outpatient Clinic, Children's hospital, Faculty of Medicine, Ain Shams University, Cairo, Egypt during the period from the beginning of May 2008 to the end of October 2010.

An informed written consent of participation in the study was signed by the parents or legal guardians of the studied subjects. This study was approved by the Bioethical Research Committee, Faculty of Medicine, Ain Shams University hospitals, Cairo, Egypt.

Study measurements:

All studied children were subjected to:

- **Medical history:** taken from the patients caregivers laying stress on neuro-developmental, perinatal and therapeutic history
- **Clinical assessment:** Including full neurological examination with special emphasis on assessment of gross motor function of patients using the GMFM-88 (Russell *et al*., 2000). In addition, Modified Ashworth Scale (Bohannon and Smith, 1987) was used to measure the degree of spasticity in our spastic CP patients (n = 44)
- **Auxological parameters:** Height was measured to the nearest 1.0 mm with a Harpenden wall mounted stadiometer and weight to the nearest 0.1 kg on electronic scales together with calculation of height for age- Standard Deviation Score (SDS) (Cole, 2002). Body Mass Index (BMI) was calculated using the formula weight (in kg)/height^2 (in meters) together with calculation of BMI SDS calculated from the age- and sex-specific reference values (Cole, 2002)
- **Tanner pubertal staging:** for assessment of pubertal status according to the standards of Tanner and Whitehouse (1976)
- **IQ assessment:** using Wechsler Intelligence Scale for Children (WISC) (Wechsler, 1991)
- **Laboratory assays:** All blood samples were taken in the morning after an overnight fast for measurement of the following:
- Basal and stimulated serum GH levels (after insulin induced hypoglycemia) which is considered the gold standard for assessment of stimulated GH levels. Baseline GH and glucose samples were withdrawn and regular insulin was administered in a dose of 0.1 unit/kg intravenously and samples for measurement of GH and glucose were withdrawn at 30, 60, 90 and 120 min. Blood glucose must decrease by 50% of the initial value or to <40 mg%. Normally, GH should rise to a peak of ≥10 ng/ml at any of the post-stimulatory samples. Patients with peak GH levels <10 ng/ml were considered GH-deficient (Greenwood *et al*., 1966). Serum GH concentrations were measured using commercial reagents (Pharmacia Diagnostics, Uppsala, Sweden) by a solid-phase, enzyme-labeled chemiluminiscent immunometric assay (by the Immulite, 2000 Analyzer, Siemens)
- Serum IGF-1 concentrations that were analyzed using commercial reagents (Incstar Corporation, Stillwater, Minnesota, USA) after extraction of the plasma samples with acid ethanol
- Serum IGFBP-3 concentrations that were measured using Diagnostic Systems Laboratories Inc, Texas, USA. Both IGF-1 and IGFBP-3 levels were measured using a solid-phase, enzyme-labeled

chemiluminiscent immunometric assay (with the Immulite, 2000 Analyzer, Siemens). Serum IGF-1 and IGFBP-3 values were compared to reference age-, sex- and pubertal stage-matched values (Teale and Marks, 1986; Juul *et al*., 1995)

Statistical analysis: The results were analyzed using the Statistical Package for the Social Science (SPSS) version number 10, Echosoft corp; USA, 2005. Description of quantitative variables was in the form of mean±standard deviation and range while that of qualitative variables was in the form of frequency and percentage. Student's t-test of 2 independent samples was used to compare 2 quantitative variables. Pearson correlation coefficient test (r-test) was used to rank different variables against each other either directly or indirectly. A p-value of <0.05 was considered significant.

RESULTS

Of 50 studied patients, 43(8%) were pre-pubertal and 7(14%) were in Tanner stage 2. Motor disabilities were found in all cases [spastic quadriplegia in 20 cases (40%), spastic diplegia in 22 cases (44%), spastic hemiplegia in 2 cases (4%) and flaccid tetraplegia in 6 cases (12%)], impaired speech in 30 cases (60%), lack of speech in 12 cases (24%), subnormal intellectual function (IQ below 70) in 42 cases [84%: 7(14%) had mild mental retardation (IQ = 50-69), 13 (26%) had moderate mental retardation (IQ = 35-49), 14 (28%) had severe mental retardation (IQ = 20-34) and 8 (16%) had profound mental retardation (IQ = <20)], seizures in 25 cases (50%), visual affection in 18 cases (36%), blindness in 5 cases (10%), impaired hearing in 15 cases (30%), deafness in 7 cases (14%) and gastrointestinal problems in 23 cases (46%). Most of children presented with 2 or more of the mentioned disabilities. Regarding the extent of motor weakness assessed by GMFM-88 scale, 36 cases (72%) had moderate to severe motor affection (levels III-V) and 14 (28%) had mild degree of motor affection (levels I-II). (Table 1).

Table 1: Frequency of various clinical findings among studied cases (n = 50)

Clinical findings	N	%
Tanner stage		
Prepubertal	43	8
Tanner stage 2	7	14
Motor disabilities		
Spastic quadriplegia	20	40
Spastic diplegia	22	44
Spastic hemiplegia	2	4
Falaccid tetraplegia	6	12
Impaired speech	30	60
Lack of speech	12	24
Subnormal IQ	42	84
Mild MR	7	14
Moderate MR	13	26
Severe MR	14	28
Profound MR	8	16
Seizures	25	50
Visual affection	18	36
Blindness	5	10
Impaired hearing	15	30
Deafness	7	14
Gastrointestinal problems	23	46
GMFM-88 scale		
Levels I-II	14	28
Levels III-V	36	72

Results are expressed as frequency and percentage. IQ: Intelligence quotient, MR: Mental retardation, GMFM: Gross Motor Function Measure. Most of children presented with 2 or more of the mentioned disabilities

Table 2: Auxological and laboratory data; and IQ of studied cases and controls

Parameters	Cases (n = 50)	Controls (n = 50)	t	p
Height SDS	-3.20±0.5 (-2.11 to -4.0)	+0.26±0.12 (-1.03 to+0.52)	25.50	0.0001***
BMI (kg/m^2)	14.33±0.56 (13.23-16.82)	17.01±0.34 (15.10-19.62)	4.39	0.041*
BMI SDS	-1.77±0.4 (-0.78 to -2.42)	-0.91±0.10 (-0.68to -1.06)	13.55	0.01*
Basal GH (ng/ml)	1.12±0.5 (0.5-2.75)	3.56±0.9 (1.15-4.18)	10.38	0.030*
Peak GH after insulin stimulation (ng/ml)	6.58±1.51 (1.10-11.87)	14.45±2.32 (10.0-18.7)	16.35	0.002**
IGF-1 (ng/ml)	96±12.80 (36.4-115.5)	132.21±10.5 (82.10-155.69)	39.69	0.0001***
IGFBP-3 (ug/ml)	3.81±1.01 (2.03-4.12)	6.25±1.13 (4.61-10.33)	15.48	0.003**
IQ	42.80±5.3 (19.2-78.5)	109.12±2.51 (90-118)	35.11	0.0001**

Results are expressed as Mean±SD and range, *p<0.05, **p<0.01, ***p<0.001, SDS: Standard deviation score, BMI: Body mass index, GH: Growth hormone, IGF-1: Insulin like growth factor-1, IGFBP-3: Insulin like growth factor binding protein-3, IQ: Intelligence quotient

All auxolgical and hormonal parameters were significantly lower among cases than controls where height SDS (-3.20±0.5 versus+0.26±0.12, respectively, p = 0.0001), BMI (14.33±0.56 kg/m^2 versus 17.01±0.34 kg/m^2, respectively, p = 0.041), BMI SDS (-1.77±0.4 versus -0.91±0.10, respectively, p = 0.01), basal (1.12±0.5 ng/ml versus 3.56±0.9 ng/ml, respectively, p = 0.03) and peak stimulated GH (6.58±1.51 ng/ml versus 14.45±2.32 ng/ml, respectively, p = 0.002); IGF-1 (96±12.80 ng/ml versus 132.21±10.5 ng/ml, respectively, p = 0.0001) and IGFBP-3 (3.81±1.01 μg/ml versus 6.25±1.13 μg/ml, respectively, p = 0.003) were significantly lower among cases than controls (Table 2). Twenty six patients (52%) were GH-deficient after insulin induced hypoglycemia, that is, their peak GH did not reach 10 ng/ml (Fig. 1a) and 31 patients (62%) had lower IGF-1 and IGFBP-3 than age- and sex- and pubertal stage-matched reference ranges (Fig. 1b). Moreover, IQ was significantly lower among cases than controls

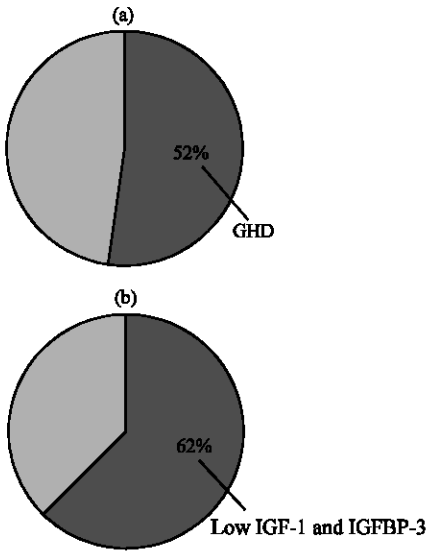

Fig. 1 (a-b): Frequency of growth hormone deficiency and reduced IGF-1 and IGFBP-3 levels among studied CP cases

Table 3: Correlation between IQ and hormonal profile among studied cases

	r	p
-Basal GH (ng/ml)	0.61	0.037
-Peak GH after insulin stimulation (ng/ml)	0.85	<0.001
-IGF-1 (ng/ml)	0.69	0.031
-IGFBP-3 (ug/ml)	0.63	0.033

IQ: intelligence quotient, GH: growth hormone, IGF-1: insulin like growth factor-1, IGFBP-3: insulin like growth factor binding protein-3

(42.80±5.3 versus 109.12±2.51, p = 0.0001, Table 2) and correlated positively with each of basal (r = 0.61, p = 0.037) and peak stimulated GH (r = 0.85, p = <0.001); IGF-1 (r = 0.69, p = 0.031) and IGFBP-3 (r = 0.63, p = 0.033, Table 3).

Among studied CP patients, height SDS (-3.66±0.21 versus -2.35±0.81, respectively, p = 0.002), basal GH (0.63±0.10 ng/ml versus 1.56±0.21 ng/ml, respectively, p = 0.04) and peak stimulated GH (3.28±1.52 ng/ml versus 8.82±1.43 ng/ml, respectively, p = 0.003); IGF-1 (58.91±4.33 ng/ml versus 87.23±7.11 ng/ml, respectively, p = 0.0001) and IGFBP-3 (2.35±0.15 μg/ml versus 3.92±0.10 μg/ml, respectively, p = 0.041) were significantly lower among those with moderate-severe muscle weakness than those with mild weakness as assessed by GMFM-88 scoring system (Table 4). In addition, GMFM score correlated negatively with each of basal (r = -0.71, p = 0.02) and peak stimulated GH (r = -0.88, p = <0.001); IGF-1 (r = -0.64, p = 0.04) and IGFBP-3 (r = -0.69, p = 0.031).

Moreover, there were significant negative correlations between the degree of spasticity assessed by Modified Ashworth Scale (Bohannon and Smith, 1987) and each of basal (r = -0.61, p = 0.032) and peak stimulated GH (r = -0.78, p = 0.01); IGF-1 (r = -0.65, p = 0.041) and IGFBP-3 (r = -0.62, p = 0.035) among spastic cases (n = 44).

Table 4: Relation between severity of muscle weakness assessed by GMFM-88 scoring system and each of auxological and laboratory data among studied cases

Parameter	Mild (n = 14)	Moderate-severe (n = 36)	t	p
Height SDS	-2.35±0.81 (-2.11 to -2.99)	-3.66±0.21 (-2.53 to -4.0)	17.21	0.002**
BMI (kg/m^2)	15.62±0.51 (14.10-16.82)	14.51±0.12 (13.23-15.91)	1.36	0.43
BMISDS	-1.35±0.41 (-0.78 to-1.81)	-1.76±0.25 (-0.99 to -2.42)	0.99	0.39
Basal GH (ng/ml)	1.56±0.21 (0.95-2.75)	0.63±0.10 (0.5-1.81)	6.18	0.040*
Peak GH after insulin stimulation (ng/ml)	8.82±1.43 (5.96-11.87)	3.28±1.52 (1.10-7.21)	18.16	0.003**
IGF-1 (ng/ml)	87.23±7.11 (75.82-115.5)	58.91±4.33 (36.4-82.56)	29.19	.0001***
IGFBP-3 (μg/ml)	3.92±0.10 (2.51-4.12)	2.35±0.15 (2.03-3.90)	4.99	0.041*

Results are expressed as Mean±SD and range, *p<0.05, **p<0.01, ***p<0.001, GMFM: Gross motor function measure, SDS: Standard deviation score, BMI: Body mass index, GH: Growth hormone, IGF-1: Insulin like growth factor-1, IGFBP-3: Insulin like growth factor binding protein

DISCUSSION

Children with CP often have poor linear growth during childhood with a high incidence of short stature and growth failure, resulting in a diminished final adult height. Poor linear growth in CP has been attributed to nutritional as well as non-nutritional factors such as those involving the neurologic or endocrine systems. Non endocrinal causes include shortening of flexor tendons, due to the lack of muscular cerebral control, but this should be responsible for causing only a slight decrease in final height. Other causes include suboptimal psychosocial deprivation and nutritional status. Spasticity might also be responsible because of increased caloric expenditure due to the excessive and continuous muscle contraction in spastic CP children. However, the number of studies in which it has been reported whether or not GH secretion is impaired in CP is quite unclear. Thus, a better understanding of the causes and mechanisms of growth impairment in CP is essential as it could lead to its prevention or treatment in some of those children (Shim *et al*., 2004).

In the present series, all auxological parameters were significantly lower among cases than controls. Similarly, Krick *et al*. (1996) studied the growth patterns of 360 children with CP and reported that on average they were 5% shorter at 2 years of age and more than 10% shorter at 8 years of age in comparison with their unaffected counterparts. In addition, Stevenson *et al*. (1994) reported growth parameters in 171 children with CP, attending an outpatient clinic in a tertiary-care setting and found that

in this population, linear growth rate declined with age, independent of nutritional status.

Moreover, in the current study, 52% of our CP patients were GH-deficient after insulin induced hypoglycemia and 62% had reduced IGF-1 and IGFBP-3 levels in comparison to age-, sex- and pubertal stage- matched reference ranges. In addition, all hormonal parameters were significantly lower among cases than controls. Although the GH-IGF-1 axis has not been systematically studied in children with CP, there have been reports suggesting abnormally low GH secretion in this population which goes with our results. Similar to our study, Coniglio *et al.* (1996) studied 10 children with CP and short stature and found that six had abnormally low spontaneous GH secretion and subnormal GH release in response to pharmacological stimulation. Also, Hayashi *et al.* (1989) reported subnormal GH responses in four males with athetoid CP after administration clonidine and in seven males with spastic CP after administration of GH-releasing hormone. Moreover, similar results were confirmed by other authors (Kuperminc *et al.*, 2009).

Based on the results of our study and on the few previous studies, we hypothesize that GH therapy could be beneficial in improving the growth velocity of GH-deficient CP children, thus improving their final height. Coniglio and Stevenson (1995) described two children with CP and linear growth failure secondary to GHD one of whom was successfully treated with GH replacement therapy. His linear growth velocity increased from 3 cm/year before therapy to 8.3 cm/year during the first two years of therapy. Potential complications such as worsening of orthopedic status did not occur and psychosocial benefits were noted. They concluded that GHD might play a role in causing linear growth failure in some children with CP and that some of these children may benefit from GH therapy which confirms present results. Also, Shim *et al.* (2004) reported a female patient with CP and short stature but without GHD who exhibited increased growth during treatment with GH. They also reported 2 other children with CP who were treated with GH: one female with a history of leukemia and a male with Klinefelter syndrome. These two children were both GH-deficient by insulin provocative GH testing and responded to treatment with increased growth rate. Growth improved to a greater extent in the two children with GHD. Thus, future studies on larger population scales and for longer durations are warranted to assess the growth benefit of GH in CP patients.

IGF-1 is responsible for most of the GH effects on longitudinal growth, but not all of them. GH is released from the anterior pituitary soon after birth; however, it does not play a significant role on longitudinal growth during the first year of life. Nutritional status is the main factor for growing during this period of life by increasing hepatic IGF-1 synthesis and release (Saxena and Moorthy, 2007). In some situations, deficient GH secretion is not accompanied by low plasma IGF-1 values; this can be observed in obese children. Childhood obesity is characterized by normal or even accelerated growth in spite of reduced GH secretion, while plasma IGF-1 levels are normal (Ballerini *et al.*, 2004; Frystyk *et al.*, 2009). A clear divergence between GH secretion and plasma IGF-1 has been reported recently in amyotrophic lateral sclerosis patients; where a marked or severe GHD exists, IGF-1 is significantly higher in these patients than in matched healthy controls (Frystyk *et al.*, 2009). Conversely, in anorexia nervosa patients, low circulating IGF-I levels are associated with enhanced GH production rate. Thus, a normal plasma IGF-1 value cannot exclude a deficient GH secretion (Scacchi *et al.*, 2003).

Recently, it was confirmed that GH plays a very important role at the central level. The GH-IGF-1 system induces neurogenesis and increases brain plasticity. GH and IGF-1 are expressed in the brain and both hormones can cross the blood-brain barrier. The GH receptor (GH-R) and the IGF-1 receptor (IGF-1-R) are widely expressed in several zones of the rodent and human brain, including the hippocampus (Chung *et al.*, 2002). In particular, GH, GH-R and IGF-1-R are expressed in hippocampal neural progenitors, acting on the proliferation and differentiation of these neural stem cells (Aberg *et al.*, 2003). Thus, besides its major role in several metabolic processes, the GH-IGF-1 axis has multiple and important neurotrophic effects, related to cell proliferation and survival, both in the central and peripheral nervous systems (Aberg *et al.*, 2006). According to this, GH-R expression is increased in the subventricular zone after focal ischemia and GH has been demonstrated to increase cell proliferation in the hippocampus of adult hipophysectomized rats (Aberg *et al.*, 2009). Similarly, IGF-1 increases cell proliferation in hippocampal cells (Christophidis *et al.*, 2009) and its expression is increased in the affected brain hemisphere after an ischemic injury. Based on the previous conclusions, children with CP were suggested to have anatomical or neurochemical abnormalities of the hypothalamic–pituitary axis that are associated both with their CP and their apparent GHD. Thus, the diagnosis of GHD should be searched for in all children with CP who are growing slowly (Gustafson *et al.*, 1999).

Moreover, in the current series, height SDS; basal and peak stimulated GH; IGF-1 and IGFBP-3 were significantly lower among cases with moderate to severe muscle weakness than those with mild muscle weakness as assessed by GMFM-88 scoring system

(Russell *et al*., 2000). In addition, GMFM-88 score correlated negatively with each of basal and peak stimulated GH; IGF-1 and IGFBP-3. The current series also demonstrated significant negative correlations between the degree of spasticity assessed by Modified Ashworth Scale (Bohannon and Smith, 1987) and each of basal and peak stimulated GH; IGF-1 and IGFBP-3 among studied cases. To the best of our knowledge, we could not trace data in literature regarding the previous issues to compare our results and so, we are the first to study such relationships. However, recently, Reimunde *et al*. (2010) tested the combined effect of GH therapy and physiotherapy for 2 months on gross motor functions in 5 CP patients with grade IV-V motor weakness having GHD and on the degree of spasticity in 5 spastic CP patients with GHD but they did not relate the GH or IGF-1 and IGFBP-3 levels to the grade of motor weakness nor to the degree of spasticity. They found a significant improvement in gross motor functions including lying, rolling, sitting, crawling, and kneeling. All these tasks are contained in the normal ontogeny of human movement, and are important to be able to perform daily activities. So, their results support our findings in the current series. Exercise is known to be a powerful stimulus for endogenous GH release, and it has been demonstrated that inhibiting PI3-Akt signaling, one of the pathways by which GH acts, blocks exercise-mediated enhancement of adult neurogenesis and synaptic plasticity in rats (Bruel-Jungerman *et al*., 2009). This may explain the lack of positive effects obtained in children undergoing exhaustive daily physical work, perhaps because possible GHD has not been determined or treated. On the other hand, it has been recently demonstrated that exogenous GH administration induces strong cellular proliferation in rodents with GHD (Aberg *et al*., 2010). In addition, Reimunde *et al*. (2010). found a significant reduction in the spasticity in 4 of their 5 spastic CP patients as measured by Modified Ashworth Scale which supports our findings. Spasticity is defined as resistance to passive movement of the joints and is a key component of the so-called upper motor neuron syndrome (Dietz, 1999). Spasticity, in its broadest clinical sense, has been linked to various motoneuronal, spinal (Nielsen *et al*., 2007) and supraspinal (Dietz, 1999), pathophysiologic phenomena. Based on the previous observation, Reimunde *et al*. (2010) assumed that the reduction in post-treatment spasticity in 4 of 5 spastic patients could be related to the efficacy of the GH treatment used to achieve normalization of the balance of supraspinal inhibitory and excitatory signals (Dietz, 1999) of the secondary structural and functional changes that occur at cellular level in the spinal cord itself below the level of the injury and/or of the voltage-dependent persistent intrinsic motoneuronal inflows (Gorassini *et al*., 2004).

In addition, for patients with CP, the beneficial effects of GH on bone metabolism could be extremely significant. GH and the mediator of its growth-promoting action, IGF-1, are key regulators of bone-cell function; they have therefore been considered as putative anabolic agents for the treatment of osteoporosis. In CP, decreased mobility and strength impair quality of life and compromise weight bearing, leading to cumulative losses in bone mineral content. In children with CP, bone mineral density averages nearly 1SD below the age-matched normal means for both the proximal parts of the femora (-0.92SDs) and the lumbar spine (-0.8SDs) (Henderson *et al*., 1995). This is clinically significant given that reduced bone density is strongly related to fracture risk. In addition to the direct effects of GH on bone, the trophic effects of GH on muscle are likely to lead to further improvement in bone health of children with CP through increased weight bearing and skeletal loading (Johannsson and Ohlsson, 1998).

Neuropsychological assessments have demonstrated that GHD is associated with reduced cognitive performance since the majority of studies found that GHD can lead to clinically relevant changes in memory, processing speed, attention, vocabulary, perceptual speed, spatial learning and in reaction time tests (Nieves-Martinez *et al*., 2010). So, in addition to the neurological deficit caused by the disease itself, part of the cognitive dysfunction observed in such patients could be related to GHD; a hypothesis that is supported by the positive correlations between IQ and each of serum basal and peak stimulated GH, IGF-I and IGFBP-3 concentrations reported in the current study.

In conclusion, GHD is prevalent in children with CP and could be one of the causes of their short stature. We propose that GH replacement therapy together with specific rehabilitation could be beneficial in prevention or correction of some of the disabilities seen in those children. Long-term controlled studies on larger population scales are needed to evaluate the benefits and safety of GH treatment in children with CP.

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