Insulin like Growth Factor-1 in Children with Cerebral Palsy

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Abstract: Background / Aim: Children with CP are generally undernourished and growth retarded. Measurement of insulin-like growth factor-1 is frequently asked in growth retarded children. The aim of the study is to assess insulin like growth factor-1 (IGF-1) as a possible non-nutritional factor for growth retardation in children with cerebral palsy (CP). **Methods:** Forty children with cerebral palsy and forty age-matched controls were enrolled. For all, serum IGF-1 & Ca level were measured by enzyme-linked immune sorbent assay (ELISA). **Results:** There was a statistically significant difference between cases and controls regarding IGF-1 with p-value <0.0001. Also, there was a significant difference in IGF-1 in relation to the height between stunted & normal with p-value 0.031, but there was no significant difference between patients and control regarding blood calcium level. **Conclusion:** Insulin like growth factor-1 deficiency is a possible non-nutritional factor for growth retardation in children with cerebral palsy (CP) especially stunted children.

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Key words: IGF-1, CP, Growth retardation.

1. Introduction

Cerebral palsy (CP) is a catastrophic acquired disease, occurring during the development of the fetal or infant's brain. It mainly affects the motor control centers of the developing brain, but can also affect cognitive functions **[Devesa et al., 2010].**

Cerebral palsy occurs in 2.0 to 2.5 per 1000 live births, there is a consistent rise in the proportion of cerebral palsy associated with preterm and very preterm births **[Reddihough et al., 2003].**

The major risk factors identified were; home and assisted delivery, consanguinity, infections and lack of antenatal care **[Bangash et al., 2014].**

The goals of management of CP children should be to use appropriate combinations of interventions (e.g., developmental, physical, medical, surgical, chemical, and technical modalities), to promote function, to prevent secondary impairments and, to increase the child's developmental capabilities **[Rosenbaum, 2003].**

Growth and nutrition disorders are common secondary health conditions in children with cerebral palsy (CP). The major causes of poor growth are malnutrition, endocrinological and environmental factors **[Kuperminc et al., 2008].**

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].**

Measurement of insulin-like growth factor 1 (IGF-1) levels is used during the assessment of a child for the presence of growth hormone (GH) deficiency and to monitor the efficacy of GH replacement therapy **[Clayton et al., 2004].**

Also in children with CP, Osteopenia is common which may be associated with lower IGF-1 level **[Ali et al., 2007].**

Insulin-like growth factor-1 is a naturally neurotrophic factor that plays an important role in promoting cell proliferation and differentiation during the normal brain development and maturation **[Bennet et al., 2003].** The major source of IGF-1 is the liver, but synthesis has been shown to take place in several other organs **[Bonefeld et al., 2011].**

In a recent study, it was indicated that diminished circulating IGF-1 and GH concentrations may explain why children with CP are smaller than normally growing children **[Kuperminc et al., 2009].**

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 et al., 2011].**

2. Subjects and Methods

Study population:

The study was a case-control study which carried out on 40 children who had cerebral palsy (22 males & 18 females) whose ages ranged between 2.5y and 13y (mean age: 5.4 ± 2.9 years). The etiology of CP was due to perinatal hypoxia in 21 patients (52.5%), prematurity in 12 patients (30%), prenatal infections in 4 patients (10%), severe hypoglycemia in 1 patient (2.5%), kernicterus in 1 patients (2.5%) and post

traumatic in 1 patients (2.5%). CP patients were studied in comparison to 40 children with normal mental & motor development (20 males and 20 females) serving as controls. Their ages ranged between 2.5 and 11 years (mean age: 6.8±2.15 years). The latter were normally growing children having no clinical findings suggesting neither endocrine disorders nor metabolic disorders. Children with history of endocrine, metabolic, or protein energy malnutrition, 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, Fayoum University, Cairo, Egypt.

Study measurements: All studied children were subjected to:

• Medical history: taken from the patients stress on neuro-developmental, perinatal and nutritional history.

• Clinical assessment: Including full neurological examination including gait, muscle tone, reflexes, power and type of CP with special emphasis on assessment of associated problems, degree of disability and severity of CP.

• Anthropometric measurements: Height, Weight, Head circumference and Mid Upper Arm Circumference of the patients were recorded for age and sex using Egyptian standard growth curves.

• Laboratory assays: All blood samples were taken for measurement of the following:

(a) Total & Ionized Ca.

(b) Insulin like growth factor-1.

Statistical analysis:

The collected data were organized, tabulated and statistically analyzed using SPSS software statistical computer package version 18 (SPSS Inc, USA). For quantitative data, the mean, median, standard deviation (SD), and range were calculated. Kolmogorov-Smirnov test (KS) test was performed as a test of normality; if variables were normally distributed independent t-test was used in comparing between two groups. In not-normally distributed variables, Mann-Whitney-U test and Kruskal-Wallis test were used as a test of significance to compare between two and three groups, respectively.

3. Results

Of 40 studied patients, Motor disabilities were found in all cases [paraplegia in 13 cases (32.5%), diplegia in 10 cases (25%), quadriplegia in 9 cases (22.5%), hemiplegic in 7 cases (17.5%) and monoplegia in 1 case (2.5%)]. Regarding tone, there was hypertonia in in 32 cases (80%), hypotonia in 5 cases (12.5%) and normal tone in 3 cases (7.5%). Regarding severity, there was 16 severe cases (40%), 13 cases with moderate severity (32.5) and 11 cases with mild severity (27.5%). there was Contracture in 31 cases (77.5%), Convulsion in 26 cases (65%), Chocking (9th & 10th CN) in 19 cases (47.5), Mental Retardation in 10 cases (25%), Hearing impairment (8th CN) in 2 cases (5%), Hydrocephalus in 1 case (2.5) and Squint (3rd CN) in 1 case (2.5%). Most of children presented with 2 or more of the mentioned disabilities. (Table 1).

All auxolgical and hormonal parameters were significantly lower among cases than controls where height mean ± SDS 97.98 ± 18.42 versus 110.75 ± 16.50, respectively, $p = 0.002$), Weight (14.94 ± 7.17 versus 19.86 ± 6.13, respectively, $p = 0.001$), IGF-1 (2.66 ± 1.30 ng/ml versus 8.05 ± 8.66 ng/ml, respectively, $p < 0.0001$), but Ca (T & I) not showed any difference between cases and controls [Total Ca (10.37 ± 0.77 versus 10.29 ± 0.53 respectively, $p = 0.586$). Ionized Ca (1.17 ± 0.06 versus 1.16 ± 0.05 respectively, $p = 0.342$). (Table 2).

Table (1): Descriptive data of the CP patients group (N=40)

	Variable	N	%
Etiology of CP	Post anoxic	21	52.5
	Preterm	12	30.0
	Post meningetic	4	10.0
	Severe hypoglycemia	1	2.5
	Post kernectric	1	2.5
	Post trumatic	1	2.5
	Paraplegic	13	32.5
	Diplegic	10	25.0
Distribution of CP	Quadriplegic	9	22.5
	Hemiplegic	7	17.5
	Monoplegic	1	2.5
	Normal	3	7.5
Tone	Hypertonic	32	80.0
	Hypotonic	5	12.5

Reflexes	Normal	4	10
	Exaggerated	36	90.0
	Mild	11	27.5
Severity	Moderate	13	32.5
	Severe	16	40.0
Complications & Cranial nerve affection	Contracture	31	77,5
	Convulsion	26	65.0
	Chocking (9th & 10th CN)	19	47.5
	Mental Retardation	10	25.0
	Hearing impairment (8th CN)	2	5.0
	Hydrocephalus	1	2.5
	Squint (3rd CN)	1	2.5

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

Variable	Cases (40)	Controls (40)	P-value
	Mean ± SD		
Weight (Kg)	14.94 ± 7.17	19.86 ± 6.13	0.001*
Height (Cm)	97.98 ± 18.42	110.75 ± 16.50	0.002*
IGF-1	2.66 ± 1.30	8.05 ± 8.66	<0.0001*
Total calcium	10.37 ± 0.77	10.29 ± 0.53	0.586
Ionized calcium	1.17 ± 0.06	1.16 ± 0.05	0.342

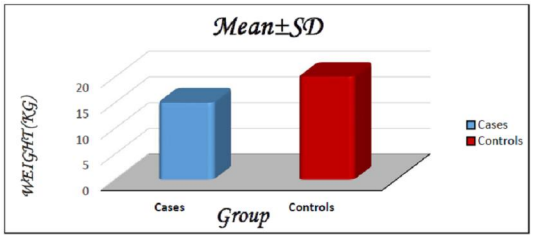

Fig. (1): Comparison between patients and control regarding weight

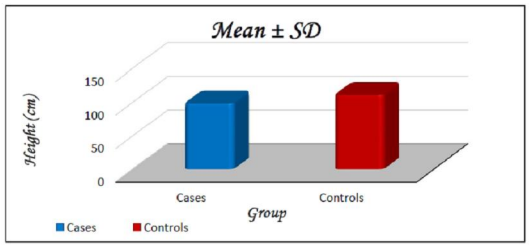

Fig. (2): Comparison between patients and control regarding height

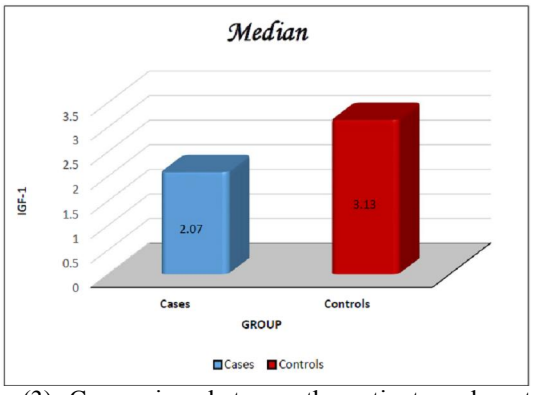

Fig. (3): Comparison between the patients and control group regarding Insulin like growth factor-1

A significant difference between cases with height ≤ third percentile and control (p=0.005) also, there was a significant difference between cases with height > third percentile and control (p=0.022). On the other hand, difference between cases with height ≤ third percentile and > third percentile was not significant (p=0.978).

Table (3): Difference in IGF-1 in relation to height

Variable	Case		Control	P-value
	≤ 3rd percentile (25)	> 3rd percentile (<25th – 5th) (15)	(40)	
	Median (range)			
IGF-1	1.97 (1.73-7.71)	2.12 (1.77-3.40)	3.13 (1.78-	0.007*

4. Discussion

Cerebral palsy can be described as a non-progressive disorder characterized by motor and postural dysfunction **(Miller, 2012).** It is a severe disability associated with abnormal growth, physical activity as well as malnutrition **(Henderson et al., 2007).** Children with CP are generally undernourished and growth retarded than normal children. Poor linear growth during childhood with a high incidence of short stature and growth failure, resulting in a diminished final adult height. The reasons for growth retardation are not only due to poor nutritional status, but also non nutritional factors including negative neurotropic effects such as depression, schizophrenia & obsessive-compulsive disorder, and indirect factors such as immobility & endocrinological abnormalities **(Yakut et al., 2006).** Other causes include 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. So 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).**It has been shown that children with CP often have poor growth during childhood. Recently, some investigators demonstrated that children with CP show deficient GH secretion, by using provocative tests for GH and their low IGF-1and GH levels may explain their low height for age and final height **(Kruse et al., 2009).** GH stimulates the production of IGF-1 in the liver, anterior pituitary gland and IGF-1-producing tissues. In the liver cells, GH activation of GH receptors induces IGF-1 gene transcription, and subsequently the synthesis and release of IGF-1 to the plasma **(Bonefeld et al., 2011).**

The high inter-individual variability in subcutaneous GH absorption & sensitivity to the drug, also the pulsatile secretion of GH don't allow the direct assessment of circulating GH level. Insulin-like growth factor -1; a key marker of GH activity has been shown to be useful in monitoring of GH level **(Pawlikowska-Haddal et al., 2012).** Also, IGF-1 is responsible for most of the GH effects on longitudinal growth. GH is released from the anterior pituitary soon after birth; however, it does not play a significant role in 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 et al, 2007).** Regarding the correlation between GH and IGF-1, **(Hegazi et al., 2012)** studied GH level after stimulation with insulin & IGF-1 hormone in 30 children with cerebral palsy in comparison with 30 healthy children and found that there was a significant correlation between GH and IGF-1 in CP patients. This study showed significant reduction in body weight & height in the cerebral palsy group compared to the matched group (In this study the weight was ranged from 6 kg to 38 kg in cases & from 12 kg to 37 kg in control study group. The height was ranged from 81 cm to 149 cm in cases & from 87 cm to 139 cm in control study group). NB: The maximum age of case is 13y & control is 11y. This study's results agreed with **(Devesa et al., 2010)** who studied growth in 46 CP children and found that they have diminished growth velocity (less than 5 cm per year) and low stature (under 3rd percentile) for their chronological age. This study's results also agreed with **(Hamaza et al., 2011)** who studied growth in 50 CP children in comparison with 50 healthy children and found that all auxological parameters were significantly lower among cases than controls. Similarly, **(Richared et al., 2007)** reported growth parameters in 171 children with CP, and found that there is decreasing in linear growth rate with age, independent of nutritional status. Additionally, **(Ellen Fung et al., 2002)** who studied 230 children with moderate to severe cerebral palsy & the results showed poor health and nutritional status regarding weight among children with moderate to severe feeding dysfunction. Similar results were observed for height. Moreover, **(Morag et al., 2010)** reported that growth problems are relatively common in CP and are most common in children with severe motor impairment. This is due to both nutrition and non-nutrition factors. This study's results revealed a statistically significant difference between cases and controls regarding IGF-1 which was lower among cases than controls. This study's results agreed with **(Hamaza et al, 2011)** who studied IGF-1 hormone in 50 CP children in comparison with 50 healthy children and found that IGF-1 significantly lower among cases than controls. This study's results also agreed with **(Devesa et al., 2010)** who studied IGF-1 hormone in 46 CP children (28 male, 18 females) aged 3 to 11 years old and stated that 31% of the patients showed low plasma IGF-1. Furthermore, the results agreed with **(Nazif et al., 2017)** who studied IGF-1 hormone in 58 children suffering from spastic CP with the age range 4-12 years compared to 19 controls and found that IGF-1 were significantly low in children with spastic CP. This study's result showed no significant differences in weight regarding chocking & also no significant difference in IGF-1 in relation to chocking. In addition, this study's result showed no significant differences in height regarding contracture and no significant difference in IGF-1 in relation to contracture. This study's results showed no significant difference in IGF-1 either in relation to severity or in distribution of CP among cases. There is also no significant Correlation between IGF-1 and study variables (age, height, weight & Ca level) among cases

& controls in this study's results. Also in This study's results, there is a significant Difference in IGF-1 in relation to height between 25 stunted cases (height ≤ 3rd percentile) & 40 control group (height > 3rd percentile). Also, there was a significant difference between cases with height > third percentile (<25th – 5th) and control group. On the other hand, difference between cases with height ≤ third percentile and > third percentile was not significant (p=0.978). This study's results agreed with the same previous study done by **(Hegazi et al, 2012)** who studied IGF-1 hormone in 30 children with cerebral palsy (7 children with normal growth (CP-N) & 23 children with retarded growth (CP-R)) in comparison with 30 healthy children and stated that IGF-1 levels were lower in CP-R group compared to CP-N and healthy children. Regarding the correlation between growth and IGF-1 hormone level, this study's results also agreed with **(Martín-Estalet al., 2016)** who revealed that IUGR infants have placental dysfunction and low circulating levels of IGF-1. Such data suggest that IGF-1 deficiency in gestational state may be one of the major causes of fetal growth retardation.

In addition, **(Wong et al., 2016)** who reviewed the growth abnormalities in children with chronic diseases & its relation to systemic abnormalities of the GH-IGF-1 axis and the role of recombinant human IGF-1 in these conditions. Regarding total & ionized calcium blood level this study's results showed no significant difference between patients and control.

The last two results agreed with **(Ali et al., 2007)** who studied 30 children (9 F and 21 M, ages 4.5–15 with CP. Subjects underwent blood tests (IGF-1 & Ca). The results showed normal calcium level & decreased IGF-1 level in CP children.

In conclusion:

Insulin-like growth factor-1 (A key marker of GH activity) showed significant level reduction among children with cerebral palsy, especially in stunted growth children.

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