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Relation Study between Chromogranin a and Other Clinical Biomarker in Iraqi Children with Growth Hormone Deficiency Undergo Treated Via Recombinant Growth Hormone

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ABSTRACT

Growth hormone deficiency is a condition that occurs when a limited volume of growth hormone is released by the pituitary gland since growth hormone deficiency causes growth delays, short stature, and overall physical development delays. symptoms differ based on the age at which they occur .Aim of this study Estimating the level of growth hormone serotonin ,IGF-1 and Chromogranin A before and after with treatment recombinant growth hormone and It is the first study in Iraq that sheds light on the relationship between Chromogranin and other variables (somatostatin, IGF-1,GH) ,also the prediction of Chromogranin A as a newly biochemical marker in children with growth hormone deficiency. In this study, 30 samples were collected from children between the ages of 4-12 years who suffer from growth hormone deficiency. Different biochemical markers are measured such as Growth Hormone (GH), Insulin-like growth factor-1(IGF-1), Serotonin, Chromogranin A. The results of measurements are compared with 30 samples of healthy children. After examining the results, it was found that the level of growth hormone was low compared to a control group, and a significant difference appeared ($P \leq 0.05$). While it was found that high levels of (IGF-1, Serotonin, Chromogranin A) of blood serum compared with the healthy group with a high-significant difference ($P<0.001$). low levels of Growth hormone and IGF-1 in the serum can be used in the diagnosis of Growth hormone deficiency.

1. INTRODUCTION

A complicated issue is the problem of growth hormone deficiency since it takes several shapes and forms that vary from one patient to another, That condition occurs when a limited volume of growth hormone is released by the pituitary gland since growth hormone deficiency causes growth delays growth hormone deficiency may have three primary factors that may be present in certain persons of which: congenital factors after birth, Acquired causes after birth, and unknown causes (1,2,3). Growth hormone deficiency (GHD) symptoms differ based on the age at which they occur. Somatomedin alterations can lead to growth hormone deficiency by two known mechanisms; tissue failure to react to somatomedin; or liver failure to produce somatomedin(4). The symptoms of hormone deficiency include Shortened stature, Slow progression, delay in puberty, Increase amount of fat around the region of the waist(5). Growth Hormone Deficiency Disease is treated as soon as the infant is diagnosed with a stimulus procedure, and treatment for growth deficiency disorder involves a daily injection of human growth hormone. Although the therapy normally lasts for many years, results can sometimes be seen 3-4 months after beginning treatment. Some children receive injections every day, and others receive injections many times a week, and although the procedure typically lasts for many years, results can often be seen 3-4 months after starting treatment (6,7). The amount of IGF-1, which is induced by development, determines the effectiveness of growth hormone replacement therapy (8). A chemical produced by nerve cells is serotonin (the pleasure hormone). It spreads messages through the cells of the nerves. Serotonin is primarily present in the digestive tract, but it is also found in platelets in the blood and in the central nervous system (9). Serotonin is made from tryptophan, an essential amino acid (10). For certain forms of cells, serotonin is also a growth factor, which can lend it a role in wound healing(11). Serotonin regulates the secretion of pituitary growth hormonewhich in turn stimulates production of insulin-like growth factors

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(IGF-1)(12),that excess serotonin may have a negative impact on the differentiation of serotonergic neurons, resulting in a decrease in the development of pituitary growth hormones (12). The Chromogranin A(CgA) is an acidic protein with a molecular weight of 48 kDa and 439 amino acids that are expressed by a variety of normal and neoplastic cells of the diffuse endocrine and neuroendocrine systems(13). CgA has been found in other secretory vesicles in endocrine, neuroendocrine, and neuronal tissues (14). CgA is also found in pancreatic islet cells, secretory granules of glucagon-containing -cells, and insulin-producing -cells, suggesting that it can modulate glucose metabolism (15). CgA is especially interesting in the form of metabolic disorders like diabetes because of this. CgA levels are higher in patients with carcinoids or other neuroendocrine tumors (16) implying that CgA plays a significant role in human health and disease (17). The insulin-like growth factor is a hormone that is equivalent to insulin in molecular composition. It controls cell division, production, and growth processes. It is also active in the glucose metabolism process (18). The pituitary and hypothalamus are linked with Insulin-like growth factor 1. That is the amount of his blood that depends on the production of other hormones. For starters, the secretion of growth hormone increases when its concentration is low. It also increases the body's released hormone output. Although with a high degree of IGF-1, there is a decrease in the release of these hormones. A direct association between somatostatin and growth factor-like insulin has been developed. The concentration of the second is rising as one of them increases (18).

2. PATIENTS AND METHODS

The study consists of two groups the First group as control (G1) consist of (30) healthy child the age range between (4 – 12) years. while the second group consist of (30) children age range between (4 – 12) years also patients that confirmed with growth hormone deficiency by giving clonidine tablets to stimulate the release of growth hormone, lowering blood sugar, and these tablets are given according to the weight, age, and height of the child, where three withdrawals take place before the stimulation and after an hour of Stimulation and after an hour and a half of stimulation, and after confirming the lack of the hormone in children Iraqis infected with deficiency growth hormone secretion after that the blood sampling was pull from patients who diagnosis as growth hormone deficiency then that parameters was measured for patients before treated with the dosage (1.5ml) recombinant growth hormone , after that this study designed to measure some parameters before treatment via growth hormone while third group (G3) belong to same children after treated with growth hormone recombinant. The cases for this study was conducted in yarmok hospital from (3 month). ,The period of time that it took to collect blood is from September to November in 2020-2021 year, Blood sampling was performed at 8.00-10.00 a.m. in the fasting state for all subjects. Five milliliters of venous blood were collected and then divided into two parts. The first section (two ml) was inserted into a tube containing an "EDTA" anticoagulant to test other parameters , while the other part (three ml) from the blood was inserted into plan tube after that was centrifuged at 3500 rpm for five minutes to obtained sera ,then storage in freezing (-20^{o}C) to the next measured parameter like Growth Hormone(DRG/ USA), Serotonin (sunlongbiotech /CHINA), Chromogranin A (sunlongbiotech /CHINA), and IGF-1(Beckman Coulter / Germany) by utilize the ELISA kit production form respectively the results was analysis by using T-test ,Mean and standard division . [Mean ±SD] and correlation relation , T-test was utilized to produce the difference between control group and patients so as between patients group before and after treatment with recombinant growth hormone .The data are compared created on given $P \leq 0.05$

3. RESULT

To describe the state of correlation between the groups, ninety enrolled participated in this study and classified into three groups control as G1, patients with GH deficiency before treated as G2 while group G3 patients with HG deficiency after treatment. Results were expressed as mean ± SD, student T.Test was used to compare between three studied groups and extraction P-value, also post t-test was utilized to show the

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difference between groups variation was considered significantly when P-values are (P≤ 0.05). Table1 describes the result of the comparison, BMI was shown in table (1) which noticed a highly-signification increase in G2 & G3 (24.9 ± 3.99) & (25.66± 4.31) when compared virus G1(17.57 ± 3.08) respectively while we show non-signification when compared between G2 VS G3, the result GH was shown in table (1) non-significant decrease when compared between G1 (0.26 ± 0.19) ng/ml Compare to G3(0.27 ± 0.24) ng/ml, while we show a significant decrease for G1 (0.26 ± 0.19) ng/ml as compared with G2(0.15 ± 0.15) ng/ml, the result Serotonin was shown in table (1) a highly-signification decrease when compared between G1 (95.05 ± 12.53) ng/ml Compare to G2 (34.53 ± 11.19) ng/ml and compared between G1 (95.05 ± 12.53)ng/ml Compare to G3 (35.84 ± 10.70), while we show non- Signification increase for G2 (34.53 ± 11.19) ng/ml as compare with G3 (35.84 ± 10.70) ng/ml, the result Chromogranin A was shown in table (1) a highly-signification decrease when compared between G1 (227.39 ± 41.13) pg/ml Compare to G2 (160.00 ± 31.17) pg/ml and compared between G1 (227.39 ± 41.13)pg/ml Compare to G3 (165.66 ± 39.42), while we show non- Signification increase for G2 (160.00 ± 31.17) pg/ml as compare with G3 (165.66 ± 39.42) pg/ml., and from the results in table (1) IGF-1 which noticed A highly-signification decrease when compared between G1 (199.33±12.91) ng/ml Compare to G3(99.6 ± 12.27) ng/ml, while we show a highly-signification decrease for G1(199.33±12.91) ng/ml as compare with G2(82.7 ± 13.12) ng/ml, and also show a highly-signification increase for G2(82.7 ± 13.12)ng/ml as compare with G3(99.6 ± 12.27) ng/ml.

Table 1: (Mean ± SD) show levels in all studied groups

Parameters	ControlG1 Mean ± SD	Patients before G2 Mean ± SD	Patients after G3 Mean ± SD	G2 VS. G1	G3 VS. G1	G2 VS. G3
Age (year)	8.86 ± 1.58	6.46 ± 1.74	6.46 ± 1.74	HS	HS	
BMI (kg/m^2)	17.57 ± 3.08	24.9 ± 3.99	25.66 ± 4.31	HS	HS	NS
GH (ng/ml)	0.26 ± 0.19	0.15 ± 0.15	0.27 ± 0.24	S	NS	S
SER (ng/ml)	95.05 ± 12.53	34.53 ± 11.19	35.84 ± 10.70	HS	HS	NS
CHGA (pg/ml)	227.39 ± 41.13	160.00 ± 31.17	165.66 ± 39.42	HS	HS	NS
IGF-1(ng/ml)	199.33±12.91	82.7 ± 13.12	99.6 ± 12.27	HS	HS	HS

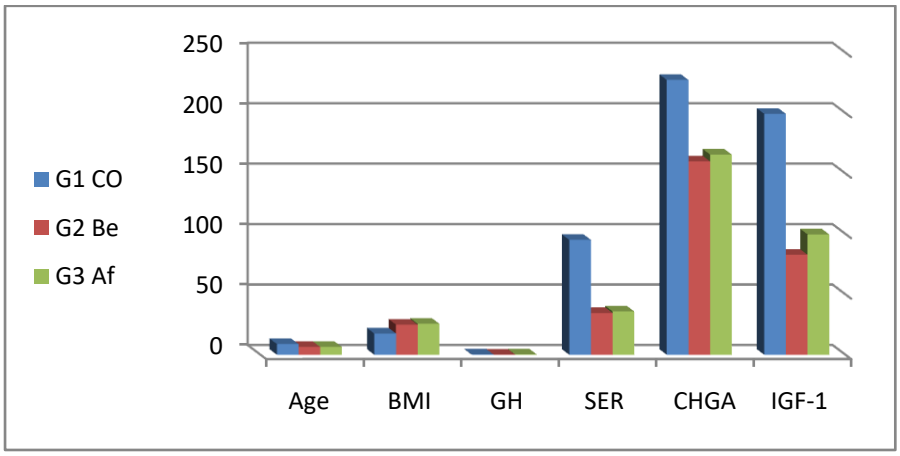

Figure 1: Compare between difference groups

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Table (2) explained the correlation between Chromogranin A and other variables in growth hormone deficiency, it appears that there is a strong negative correlation between Chromogranin A with (GH,IGF-1,Age) parameters while the strong positive correlation with (BMI, Serotonin) parameters.

Table2: Correlations between Chromogranin A and other variables in growth hormone deficiency.

Correlation parameters	Groups			
	G2		G3	
	r	P	r	P
AgeVS. CHGA	-0.309	HS	-0.212	HS
BMI VS. CHGA	0.21	HS	0.0312	HS
Growth Hormone VS. CHGA	-0.014	HS	0.186	HS
Serotonin VS.CHGA	0.128	HS	0.137	HS
IGF-1 VS. CHGA	-0.173	HS	-0.0182	HS

4. DISCUSSION

This research differs from those that have been noticed. Growth hormone has an effect on the human body's makeup. Growth hormone deficiency (GHD) is characterized by an increase in body fat mass and a decrease in lean body mass, including muscle mass (19). During the use of recombinant human growth hormone therapy (rhGH), the patient's muscle mass and bone density strengthen, improving the patient's quality of life (20) As a consequence, growth hormone is essential to the body's structure and function. It has an anabolic effect on skeletal muscles, which promotes bone development and mineralization,it also stimulates protein metabolism(21). As well as another study that There was no significant difference in the height velocity regarding the sex, age, partial or complete GHD and the degree of the bone age delay in contrast to a birth weight which had a significant positive correlation with height velocity response. This study indicates a significant response in linear growth in patients with GHD after treatment with recombinant GH with positive relationship with birth weight (22). Chromogranin A is a biomarker for predicting GHD in children and also the neuroendocrine marker is Chromogranin A(23), Because CgA has been found in neuroendocrine (24,25), which often in the absence of other biochemical markers of the disease is a useful factor in both the diagnosis and monitoring of disease(26,27). Serotonin regulates the secretion of pituitary growth hormone which in turn stimulates production of insulin-like growth factors (IGFs). The most recent literature shows the possible negative influ ence of serotonin in excess on differentiation of serotonergic neurons with consequent reduction in pituitary growth hormone production, which has a direct effect on hepatic production of IGF-I, particularly in the post-natal period (12). It was agreed with this study that growth hormone and insulin-like growth factor decrease in children who suffer from growth hormone deficiency, and as this study showed that there is a relationship between leptin hormone and the regulation of growth hormone secretion and the concentration of insulin-like growth factor(IGF-I)(28).

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5. CONCLUSIONS

In this study that was conducted on 60 Iraqi children aged 4-12 years, it was found that low levels of (GH, IGF-1) and high levels of (Chromogranin A, Serotonin) in the serum can be used in the diagnosis. Growth hormone deficiency.

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