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Evaluation of Some Biochemical and Hematological Parameters in Serum of Children with Short Stature

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KEYWORDS
Short stature, Growth Hormone, Tissue Transglutaminase

ABSTRACT:

Background: Short stature (SS) is defined as an individual's height being below by more than twice the standard deviation (SD) of the average height of a given sex and age or the height is less than the third percentile of his or her peers.

Methods: Serum growth hormone (GH) , growth hormone stimulating test (GHST), tissue transglutaminase – IgA **(**tTG-IgA) , tTG-IgG, Anti-Gliadin Antibody-IgA (AGA-IgA), and AGA-IgG concentrations were assayed by sandwich ELISA technique, also hemoglobin (Hb), percentage of packed blood cell volume (PCV%) , erythrocyte sedimentation rate (ESR) and white blood cells (WBC) count were estimated in 30 healthy children as a control group and 60 patients with short stature, age range (5 - 14) years.

Purpose: This study aimed to evaluate some biochemical and hematological parameters to determine the extent to which the parameters are affected by this disease, which reflect function imbalance of the relevant organs, and to use it as a diagnostic tool that helps in the early treatment and follow-up of the disease.

Results: The results showed a significant decrease ($p \leq 0.01$), with percentages (26.6) % in GHST and a significant decrease ($p \leq 0.05$) by (15.7) % in WBC count, while a significant increase ($p \leq 0.05$) by (540) % in AGA-IgG in patients with short stature compared to healthy children. GH, tTG-IgG, AGA-IgA, Hb, PCV% and ESR did not show significant differences. Gender and age did not show a clear effect on most of studied parameters**.**

Conclusions: It appears that, determination of GHST and AGA-IgG in children with short stature is a potentially useful marker in the management of this disease.

INTRODUCTION

Short stature (SS) is defined as a child's height being shorter by more than twice the standard deviation (SD) of the average height of children of the same sex and age. A child is also considered short stature when his height is less than the third percentile on the growth chart assigned to gender. About 80% of children are diagnosed with idiopathic short stature (ISS) in the absence of growth hormone (GH), disorders in endocrine glands or organ systems, and genetic problems. Various studies have recorded the effect of short stature on the quality of life in children, as a child's stature is evidence of his physical health, and therefore short stature has a significant impact on the child's mental health and he is more susceptible to social and psychological problems such as lack of self-confidence, depression, slow learning, and exposure to bullying. Children who live at a low economic level also suffer from weak growth due to the lack of health care [1] [2].

Growth hormone (GH), also called somatotropin, is 191 amino acids- peptide chain with a molecular weight (20-22) kilodaltons. It is produced by somatotropes in adenohypophysis, and secreted into the blood in a pulsating manner.It is stimulated by growth hormone- releasing hormone (GHRH) and inhibited by somatostatin, both of the latter hormones are produced in the hypothalamus [3].

All anterior pituitary hormones, except growth hormone, perform their main work by stimulating the

Journal of Chemical Health Risks

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target glands, while growth hormone has a direct effect, as it increases cell size, division process, development and differentiation of a large number of cells in several tissues in the body, including the liver, cartilage, bones, muscles, and adipose tissue [4]. In cartilage and muscles, it stimulates the absorption of amino acids, protein and collagen synthesis, as well as increases the number and size of cells. As for adipose tissue, it increases the breakdown of fatty acids and reduces glucose absorption, so sometimes referred to as the anti-insulin effect [5].

Growth hormone deficiency occurs in 10% of short people when the pituitary gland fails to produce sufficient quantities of hormones that regulate vital functions in the body, including growth hormone. This deficiency may be separate or part of a condition known as multiple pituitary hormone deficiencies (MPHD). In rare cases, a complete absence of growth hormone may occur, but usually an insufficient hormone [6]. Tumors in the pituitary and hypothalamus also have an effect on the regulation of the endocrine glands, either directly or secondarily due to treatment such as surgery and radiotherapy [7]. Growth failure is one of the first signs of an endocrine disorder or growth hormone deficiency [8]. This deficiency not only affects body growth, but it also affects brain maturation and some behavioral studies link growth hormone deficiency in children with various psychological and cognitive problems [9].

Growth hormone deficiency occurs for several reasons, including genetic and congenital causes such as complete pituitary absence, pituitary hypoplasia, GH-1 mutations, GHRH receptor mutations, and Pit-1/Prop-1 mutations or acquired causes such as tumors of the central nervous system, exposure of the skull to radiation, medication, head injury and inflammatory diseases. As well as accidental causes, including hypothyroidism, delayed puberty, and psychological problems [10] [11].

Celiac disease (CD) is one of the important causes of short stature, which is sometimes accompanied by anemia, diarrhea, vomiting, abdominal pain and distention [12]. The percentages of the SS infected with the CD is estimated about 10.9% respectively around the world, and its prevalence varies depending on the geographical region and ethnic groups [13]. This disease affects people who are allergic to gluten, a protein composes of glutenin and Gliadin, found in grains such as wheat, rye and barley. CD is characterized by various associations between damage to the small intestine (flattened villi) and antibodies formed during the disease [14].

MATERIALS AND METHOD

In all patients with Short stature and controls, 5 ml of blood was obtained from peripheral venous and divided into two parts, 3 ml dispensed into EDTA tube to estimate hemoglobin (Hb), packed cell volume (PCV), white blood cells count (WBCs) and erythrocyte sedimentation rate (ESR) by auto hematology analyzer, while 2ml dispensed into plain tube, leaved at 37 °C for 20 min., then centrifuged at 3000 rpm and sample sera were pipetted off and stored at - 20°C.

Serum growth hormone (GH) concentration was estimated by sandwich ELISA technique kit that was provided by SunLong Biotech Co., LTD., from China. Growth hormone stimulation test (GHST) mediated by Clonidine and the test was performed by taking the initial baseline sample from the patient after fasting and assessing the growth hormone at zero time, then the patient was given clonidine orally at a concentration of (5) micrograms per kilogram of body weight, the dose given should not exceed (250) micrograms, and after waiting an hour and a half, the second blood sample was taken and the growth hormone was re-assessed again. The concentrations of tTG-IgA, tTG-IgG, G-IgA and G-IgG antibodies in serum were estimated using sandwich ELISA technique kit (S-ELISA) that was provided by AESKULISA, from Germany

All parameters were estimated in patients (n=60) with Short Stature from Al-Wafa Center for Diabetes and Endocrinology in Mosul city, as well as (30) healthy children as a control group, equally divided into both sexes, and their ages ranged from (5-14) years from (September 2022 - February 2023).The patients and control were divided into two age groups (<10 and >10) years.

The results were statistically analyzed using SSPS program, version (23), based on the T-test and Duncan's multiple range test. Result values were expressed using mean (M) ± standard deviation (SD). To determine statistically significant differences, we relied

Journal of Chemical Health Risks

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JCHR (2023) 13(3), 890-897 | ISSN:2251-6727

on two levels of probability, $p \leq 0.05$* and $p \leq 0.01$** [15].

RESULTS

It was found through this current study that there are different effects of short stature on the studied parameters. Table (1) shows a significant decrease at the probability level ($p \leq 0.01$) in growth hormone stimulation test (GHST) in patients with short stature compared to the control group (10.4 ± 4.2) ng/ml and (14.2 ± 2.3) ng/ml respectively. While a significant increase ($p \leq 0.01$) was observed in the level of Anti-Gliadin Antibody-IgG (AGA-IgG) IU/ml in patients with short stature (19.1 ± 32.68) IU/ml compared to the control group (2.9 ± 1.1) IU/ml. Growth hormone, tissue transglutaminase – IgA (tTG-IgA) and (tTG-IgG), Anti-Gliadin Antibody-IgA (AGA-IgA did not show a significant difference.

Regarding hematological parameters, it is clear from table (1) that there was a significant decrease ($p \leq 0.05$) in WBCs count (5.9 ± 1.4) $x10^3$ /µL in patients with short stature compared to the control group (7.02 ± 1.8) $x10^3$ /µL ,while hemoglobin, percentage of packed blood cell volume (PCV%) and erythrocyte sedimentation rate (ESR) did not show significant differences.

Table 1. Values of biochemical and hematological parameters in short stature patients compared to control group.

Parameters	Control n=30 M±SD	Patients n=60 M±SD	Percentage change
Growth Hormone (GH) ng/ml	1.75 ± 0.5	1.84 ± 1.1	+ 5.2%
Growth Hormone Stimulation Test (GHST) ng/ml	14.2 ± 2.3	10.4 ± 4.2**	-26.6%
Tissue Transglutaminase-IgA (tTG-IgA) IU/ml	3.1 ± 1.6	6.5 ± 15.2	+110.2%
Tissue Transglutaminase-IgG (tTG-IgG) IU/ml	2.6 ± 0.7	4.1 ± 5.3	+56.6 %
Anti-Gliadin Antibody-IgA (AGA-IgA) IU/ml	2.6 ± 0.5	9.2 ± 23.6	+253.4%
Anti-Gliadin Antibody-IgG (AGA-IgG) IU/ml	2.9 ± 1.1	19.1± 32.68**	+540%
Hemoglobin (Hb) g/dl	12.14 ± 0.65	11.93 ± 1.1	-1.8%
Packed Cell Volume (PCV) %	38 ± 2.05	37 ± 3.2	-2.8%
White Blood Cell (WBCs) $x10^3$ / µl	7.02 ± 1.8	5.9 ± 1.4*	-15.7%
Erythrocyte Sedimentation Rate (ESR) mm/hr.	9.4 ± 3.3	9.09 ± 4.5	-3.9%

* means that there is a significant difference at the probability level ($p \leq 0.05$).

* * means that there is a significant difference at the probability level ($p \leq 0.01$).

It is noted from the results of our study that some of the biochemical and hematological parameters were affected by short stature, while others did not. In addition, it was noted that not all children with short stature showed these changes in those parameters. Table (2) showed the percentage of the number of children with short stature in whom the concentrations of the studied parameters were within and out of the normal range.

Table 2. Percentage of children's number with short stature and their concentration of biochemical and hematological parameters within and outside the normal range.

Parameters	Normal range (NR)	Patients within NR Mean ± SD	Number's percentage	Patients out of NR Mean ± SD	Number's percentage

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(3), 890-897 | ISSN:2251-6727

Growth Hormone (GH) ng/ml	0.72-2.78	1.6 ± 0.5	79%	0.15 ± 0.07	21%
Growth Hormone stimulation Test (GHST) ng/ml	9.4-18.9	13.5 ± 2.7	55%	6.6 ± 1.9	%45
Tissue Transglutaminase-IgA (tTG-IgA) IU/ml	0.1-6.3	3.05 ± 1.3	%82	77.5 ± 22.5	%18
Tissue Transglutaminase-IgG (tTG-IgG) IU/ml	1.1-4.2	2.4 ± 0.8	%90	19.3 ± 3.7	%10
Anti-Gliadin Antibody-IgA (AGA-IgA) IU/ml	1.4-3.7	2.5 ± 0.4	%82	88.5 ± 10.5	%18
Anti-Gliadin Antibody-IgG (AGA-IgG) IU/ml	0.6-5.3	2.4 ± 0.8	%71	84.3 ± 11.14	%29
Hemoglobin (Hb) g/dl	10.8-13.4	12.16 ± 0.6	89%	9.3 ± 1.4	%11
Packed Cell Volume (PCV) %	34-42	37.5 ± 1.9	90%	31 ± 1.15	%10
White Blood Cell (WBC) $x10^3$ /µl	4.5-10.1	6.3 ± 1.2	79%	4.1 ± 0.2	%21
Erythrocyte Sedimentation Rate (ESR) mm/hr.	4.6-15	8.7 ± 2.5	%91	3.3 ± 0.4	%9

DISCUSION

It was observed from table (2) that 79% of patients with short stature had growth hormone levels within the normal range, and this was confirmed by some studies [16] [17], and sometimes an increase in growth hormone is observed in children with idiopathic short stature [18]. The reason for this variation in growth hormone levels is attributed to its pulsatile or rhythmic pattern of secretion [19].

Growth hormone is secreted in bursts, and its peak secretion occurs during times of deep sleep, from (2-4) am [20] [21]. Based on the above, the growth hormone stimulation test (GHST) is relied upon to determine the actual level of growth hormone and by observing the results in table (1), it was shown that 24% of the children whose growth hormone level appeared to be normal showed a significant decrease in it compared to the control group when GHST was performed, bringing the actual percentage of children who had a normal level of growth hormone to 55% despite their short stature. The reason for this is due to the possibility of growth hormone insensitivity in these patients [22] [23], which may be caused by many reasons including a mutation in hormone receptors (such as Arg161Cys, Arg211His and Glu224Asp) [24] [25], hypothalamic damage , perhaps due to cranial irradiation [26], presence of a condition called bioinactive growth hormone (BGH), in which the synthesis of the hormone is abnormal, which in turn reduces the hormone's affinity for its binding protein or its receptor [27].

The results in table (2) showed that about 20% of patients had an increase in the concentrations of antibodies associated with celiac disease (CD), this indicates that the possibility of the cause of short stature in these children being due to this disease. The reason we mentioned the possibility of short stature and not confirmed it is due to some studies indicated that antibody tests are preliminary tests, and in order to reach a more accurate diagnosis of the disease, it is preferable to perform a histological examination of the intestine (bowel biopsy) in the event of positive antibody tests [28] [29] , while recent studies mentioned that there is no need to conduct a histological examination and that antibody tests are sufficient when they exceed the normal limit[30] [31].

Some studies also indicated the necessity of assessing total serum IgA in patients with celiac disease who have clear symptoms and whose examination results were negative for the (tTG-IgA) or (AGA-IgA) tests, because IgA deficiency gives false-negative results [32] [33].

It was noted from table (1) that the concentrations of tissue transglutaminase-IgA(tTG-IgA) and tissue transglutaminase-IgG(tTG-IgG) reached approximately

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(3), 890-897 | ISSN:2251-6727

double in patients compared to the control group, and it appears from previous studies that the concentrations of these antibodies can reach ten times in patients with celiac disease [34].

It was clear from table (2) that only (10%) of the children with short stature had anemia, and this result was almost identical to the study of El-Shafie *et al* which was conducted on children with short stature in the primary stage (age 6-11 years), as the percentage of those suffering from anemia was only (9.9%) [35] . This result is also consistent with other studies conducted in many middle-income countries [36].

In fact, previous studies mentioned the possibility of a relationship between complete blood cell count (CBC) and short stature, but it is an indirect relationship (not permanent) [37], as the relationship depends on the causes that lead to short stature, such as kidney failure, nutritional deficiency, and other causes [38].

Some studies also indicated that children with thalassemia major and sickle cell anemia are more likely to suffer from short stature and a disorder of growth hormone-insulin-like growth factor I axis (GH-IGF-1 axis) than others [39] [40] , and other studies have indicated that children with thalassemia major suffer from growth failure represented by short stature , underweight and delayed puberty due to decreased hemoglobin and packed cell volume (PCV %) [41] [42] [43].

Some studies have also indicated a relationship between the growth process and Diamond-Blackfan anemia (DBA), which is a hereditary disease that causes failure of the bone marrow to produce blood, and the healthy condition of these patients improved when they were treated with growth hormone , hematopoietic cell transplantation or gene therapy [44] [45]. Another study indicated that iron deficiency anemia could be a risk factor for short stature [46].

Regarding the white blood cell count, it is noted from Table (2) that (21%) of the patients showed a decreased number of these cells, and this result is consistent with previous studies that showed that anemia associated with a deficiency of white blood cells could include short stature as one of its complications [47].

Many studies indicated to a pathological condition known as pancytopenia, condition in which erythropenia, leucopenia, and thrombocytopenia coexist, which occur for various reasons such as inherited bone marrow failure syndromes, immune disorders, infections, nutritional deficiencies, and cancer [48] [49].

Some studies indicated that pancytopenia in celiac disease causes short stature in children, and the reason is attributed to the possibility of T cells affecting or destroying tissues [50] [51] [52].

In general the medical tests should be performed for people who suffer from chronic abdominal pain, bloating, chronic intermittent diarrhea, headaches and extreme fatigue, calcium deficiency and osteoporosis and anemia due to severe iron and vitamin deficiency which leads to growth failure, weight loss, short stature, and absence of menstruation. Amenorrhea and delayed puberty [53].

CONCLUSION

From this report it appears that, determination of growth hormone stimulation test (GHST) and Anti-Gliadin Antibody-IgG(AGA-IgG) and some hematological parameters in patients with short stature are potentially useful markers in the management of celiac disease (CD).

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ETHICAL STATEMENT

The Ministry of Health and Environment's ethical commission gave its approval to this study.

CONFLICT OF INTEREST

The authors affirm that they do not have any competing interests.

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