Journal Homepage: -www.journalijar.com
INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)
Article DOI:10.21474/IJAR01/8913
DOI URL: http://dx.doi.org/10.21474/IJAR01/8913

RESEARCH ARTICLE

THE SIGNIFICANCE OF LABORATORY CLASSIFICATION OF ISOLATED GROWTH HORMONE DEFICIENCY.

Dr. Shamil A. Sharba.
Department of pediatrics, college of medicine, University of Kufa.

Manuscript Info

Manuscript History
Received: 20 February 2019
Final Accepted: 22 March 2019
Published: April 2019

Key words:-
Growth hormone deficiency, GHD, short stature.

Abstract

Background: Short Stature (SS) is defined as a standing height more than 2 standard deviations (SDs) below the mean (or below the 2.5 percentile) for sex. Causes of short stature include familial short stature, constitutional delay, endocrinopathies (e.g. Growth Hormone Deficiency), chronic systemic diseases and syndromic causes of SS.
Aim of the study: To show the significance of the laboratory classification of isolated GHD to help for adjustment of dosages and duration of GH treatment.
Methods:A retrospective study of children with isolated Growth Hormone Deficiency (GHD) who have been registered in GH Unit in the Al-Zahraa teaching hospital for Maternity and Children at Al Najaf city, Iraq from March 2012 to September 2016. A total number of 122 patients included in this study all of them on GH replacement .The population study were classified according to post-stimulation peak serum GH level into Mild GHD (>8 − <10ng/ml) ,Moderate GHD (≥5 − ≤ 8ng/ml) and Severe GHD (< 5ng/ml). The cases also grouped according to age into 3 age groups (Group A: < 6 years, Group B: ≥ 6 − <11 years and Group C: ≥11years), sex and residency. In each of these age groups, comparison done between Mild, Moderate and severe isolated GHD.
Results: This study showed that in Group A (35 cases) there was no statistically significant difference between Mild, Moderate and Severe isolated GHD regarding pre-treatment height and rate of the height velocity after the first year of GH treatment (p-value=0.6 for pre-treatment height and 0.74 for rate of height velocity H.V.). In Group B (50 cases) and Group C (37 cases) also no statistically significant difference, Group B (p-value=0.53 for pre-treatment height and p-value= 0.92 for H.V.) and Group C (p-value=0.63 for pre-treatment height, p-value= 0.92 for H.V.)
Conclusion: No significance of classification of short stature children with isolated GHD according to stimulated peak GH value with cut-off less 10 ng/ml.

Corresponding Author:-Shamil A. Sharba.
Address:-Department of pediatrics, college of medicine, University of Kufa.

Introduction:-

Short stature is defined as a standing height more than 2 standard deviations (SDs) below the mean (or below the 2.5 percentile) for sex.[1] the clinical approach to patients with short stature start with a history and physical examination, anthropometric measure, and follow up of growth velocity, midparental height, and bone age.[2]
Short Stature could be normal variations of growth or Familial which associated with family history of short or constitutional growth delay which often associated with family history of being a "late bloomer**"**. The bone age always delayed, often corresponding to height age. Slowed growth velocity during the first 3 years of life, but normal or near-normal growth velocity during the rest of childhood**.** Short stature could idiopathic or due to endocrinopathies such as growth hormone deficiency or growth hormone insensitivity or due to hypothyroidism, glucocorticoid excess, chronic Systemic Disease, malnutrition or gastrointestinal disease (e.g. Malabsorption, inflammatory bowel disease, psychosocial dwarfism. Syndromic Causes of Short Stature like Skeletal Dysplasia (e.g. achondroplasia**)** , Turner Syndrome and others were associated with short stature.[3, 4]

Growth hormone is a stress substance that increases the serum level of glucose and serum level of free fatty acids. [5]
Growth hormone is the human chorionic somato-mammotropin, and prolactin were belong to a group of hormones that promote growth and lactogenic activity. [6, 7]

Growth hormone release from the pituitary gland and primarily determined by the equilibrium of these two substances, that will affected by several physiological stimulators like exercise, nutrition, sleep and inhibitors of GH secretion like free fatty acids. [8]

The serum level of GH during these levels may range from 5 to even 45 ng/mL. Between the peaks, basal GH levels are low, usually less than 5 ng/mL for most of the day and night. [9]

The growth hormone is the most common hormone deficiency of pituitary gland and it may be of congenital or acquired etiology, however the majority of conditions are idiopathic. [10]

The golden method to diagnose GH deficiency is to measure the responses to GH to provocation challenge. The cut value to define GH deficiency is serum peak GH concentration <10 ng/mL on a challenge with at least two separate stimulation test. [11]

GH stimulation tests are performed with various stimuli, such as insulin, L-dopa, arginine, and growth hormone releasing hormone (GHRH). [12]

Treatment of GHD includes growth hormone injections that given at home. The shots are most often given once a day. Older children can often learn how to give themselves the shot. [13]
In childhood, the recommended dose of hGH is 0.18-0.3 mg/kg/wk but higher doses should be used in puberty. Recominant GH is given subcutaneously in 6 to 7 divided doses. The maximal response occurs in the first year of treatment, and growth velocity during this 1st year is typically above 95th percentile for age. With each successive year of treatment ,the growth rate tends to decrease. [14]
It is vital to start the treatment as easy as possible so we can reach normal height with GH therapy before the onset of puberty. [15]

The aim of this study is to evaluate significance of the laboratory classification of isolated GHD to help for adjustment of dosage and duration of GH treatment and to assess the correlation with the height deficit before treatment.

Patients and Methods

Study Design

A retrospective selective study was performed on 122 short stature children with isolated Growth Hormone Deficiency who have been registered in Growth Hormone Unit in Al Zahraa Teaching Hospital for Maternity and Children at Al Najaf city, Iraq from March 2012 into September 2016. A total of 290 short stature cases registered in Growth Hormone Unit were analyzed, 122 cases were included in the study, and 168 cases were excluded according to the inclusion and exclusion criteria, respectively. The cases were classified according to sex (Male, Female), residency (Urban, Rural) and age into 3 age groups: Group A; < 6 years, Group B; ≥6 − < 11 years and Group C; ≥ 11 years. Again the cases were classified according to the post-stimulation peak serum GH level into 3 groups: mild,

moderate and severe GHD: Mild GHD (≥8 ng /ml- < 10 ng /ml), Moderate GHD (≥5 ng /ml -<8 ng /ml) and Severe GHD (<5 ng /ml).And Mild Moderate and Severe GHD were distributed according to sex, age group and residency.

Inclusion criteria:-

1. Short stature cases who have been diagnosed with isolated GHD (post-stimulation GH level < 10 ng / ml).
2. cases completed the 1 year of regular GH replacement.

Exclusion criteria:-

1. cases not completed 1 year of GH replacement.
2. cases with irregular visits to or lost the contact with GH Unit.

Data Collection

The data was obtained from the case sheets of 122 short stature patients with isolated GHD who were registered in GH Unit. The information collected includes: Sex, residency, age at diagnosis, initial body weight and height at diagnosis and at each follow-up visit at regular intervals, x-ray for bone age, serum basal GH level, serum peak post-stimulation GH level, rate of the height velocity during the first year of GH replacement.

The short children have consulted GH Unit, evaluated by history and physical exam , measurement of height with comparison to gender and age , specifically investigating presence of chronic diseases, other endocrine or dysmorphic genetic disorders e.g. screening tests for hypothyroidism and celiac disease and radiological evaluation by bone age estimation from x-ray of left wrist and hand.

The cases diagnosed to have isolated GHD from assessment of peak serum GH value after provocation test in the hospital laboratory, by using clonidine tab single dose orally taken at same time with measuring of basal serum GH level, then 1hr later, peak stimulated serum GH level was measured .

Serum GH was measured with ELIZA test using commercial ELIZA kit, made in Italy, the cut-off value for this kit is 10 ng/ml, patients with stimulated value less than 10ng/ml was considered GH-deficient.

Recombinant GH was given to all patients in a dose of **0.3 mg/kg/wk** divided daily at bed time given by SC route with close supervision at the beginning of therapy.

The cases had 2 monthly regular follow-up visits to GH Unit for checking. In each visit physical examination was done in addition to anthropometric measurements to assess the response to GH therapy and possible side effects

Statistical analysis

Data was collected and analyzed by Excel from Microsoft 2010 and SPSS from IBM version 21.We used ANOVA test for comparision among groups where p-value < 0.05 considered significant.

1. The rate of the height velocity during 1st year of GH therapy was calculated.
2. The Z-score of the height for age at time of diagnosis was measured using WHO anthropometric measure.
3. In each of the 3 age groups (A,B and C), a comparison was made between mild ,moderate, and severe GH Deficiency according to Z-score of the height for age at time of the diagnosis and rate of the height velocity during first year of GH replacement

Results

In this retrospective selective study,a total number of 122 short stature children with isolated GH deficiency .They were 76 males (62.29%) vs 46 females (37.71%), 98(80.32%) living in urban area vs 24 (19.68%) in rural area.According to age, GroupA was 35 (28.68%), Group B was 50 (40.98%) and Group C was 37 (30.32%) .

Table 1:-Descriptive characteristics of all study population

Parameter	Mean	SD	No.	**%**
Age(yeas)				
Group A	4.6	0.91 ±	35	28.68
Group B	8.2	±1.42	50	40.98
Group C	13.5	± 1.63	37	30.32
Severity of GHD(ng/ml)				

Mild GHD	8.7	± 0.72	5	4.05
Moderate GHD	6.1	±0.97	15	12.29
Severe GHD	1.76	±1.2	102	83.66
Growth Velocity during 1st year(cm) of treatment	7.2	2.3 ±		
Z-score of height for age at time of diagnosis	3.2	± 1.43		

Table 2:-Gender, residency and groups distribution of Mild, Moderate and Severe GHD

	Mild GHD		Moderate GHD		Severe GHD		P-value
	N	**%**	N	%	N	%	
Gender							
Male	2	40	10	66.6	64	62.74	0.552
Female	3	60	5	33.3	38	37.26	
Residency							
Urban	4	80	11	73.33	83	81.37	0.765
Rural	1	20	4	26.67	19	18.63	
Groups							
GroupA (< 6 years)	1	20	4	26.6	30	29.41	0.88
Group B (≥6- < 11 years)	2	40	5	33.3	43	42.15	
Group C(≥ 11 years)	2	40	6	40	29	28.43	

Table(2) illustrated that there was no statistically significant difference between Mild,Moderate and Severe GHD regarding the gender (p-value=0.552), the residency (p-value=0.765), the age group (p-value=0. 88).

Table 3:-Comparison between Mild, Moderate and Severe GHD in Group A

		Stimulated GH level	Z score	Velocity
Severe GH deficiency	mean	1.5	-2.97	6.8
Moderate GH deficiency	mean	5.90	-3.52	8.70
Mild GH deficiency mean		9.5	-2.6	5.5
P-value		0.000	0.6	0.74

Table(3) illustrated that in Group A (n=35, Mean age=4.6 and SD = ±0.91) there was no statistically significant correlation between Mild, Moderate and Severe GHD according to Z-score of the height for age at time of diagnosis and rate of height velocity after the 1st year of GH therapy(p-value= 0.6 for Z-score and 0.74 for height velocity).

Table 4:-Comparison between Mild,Moderate and Severe GHD in Group B

		Stimulated GH level	Z score	Velocity
Severe GH deficiency	Mean	2	-3.3	7.7
Moderate GH deficiency	Mean	6.8	-4	7.4
Mild GH deficiency	mean	8.75	-2.5	8.25
P-value		0.000	0.53	0.92

Table(4) illustrated that in Group B (n= 50 , Mean age 8.2 = and SD=±1.42) there was no statistically significant correlation between Mild,Moderate and Severe GHD according to Z-score of the height for age at time of diagnosis and rate of height velocity after the 1st year of GH therapy (p-value =0.53 for Z-score and 0.92 for height velocity).

Table 5:-Comparison between Mild,Moderate and Severe GHD in Group C

		Stimulated GH level	Z score	Velocity
Severe GH deficiency	mean	1.7	-3.5	6.6
Moderate GH deficiency	mean	5.8	-3.2	7.8
Mild GH deficiency	mean	8.4	-4.25	7.5
P-value		0.000	0.63	0.53

This table(5) illustrated that in Group C (n=37, Mean age = 13.59 and SD= ±1.63) there was no statistically significant correlation between Mild,Moderate and Severe GHD according to Z-score of the height for age at time of diagnosis and rate of height velocity during 1st year of GH therapy (p-value= 0.63 for Z-score and 0.53 for height velocity).

Discussion:-

More than 50% of patients receiving growth hormone therapy is due to idiopathic cause of deficiency. The aim of the therapy is to reach normal growth. (16)

The response to GH treatment is assessed every 3-6 months by sequential height determinations and by occasional bone age, the most important reasons for the follow-up are to monitor growth progress and to adjust GH dosage. Growth rate usually increases during first year of treatment (catch-up growth) and then slows down over

The present study has classified 122 short children with isolated GHD according to peak GH response to stimulation test into mild(≥8 ng /ml - < 10 ng /ml) , moderate(≥5 ng /ml - <8 ng /ml) and severe(<5 ng /ml) to evaluate the correlation of severity of GHD with the response to the treatment during this catch-up growth period to adjust GH dosage and duration if needed and with the height deficit at time of diagnosis .

The results have shown no statistical significance of this laboratory classification of isolated GHD, in all short children age groups(Group A,B and C) , the rate of height velocity on treatment and baseline (pre-treatment) height were unrelated to severity of GHD, that outlined by this laboratory classification.

In Group A (< 6 years), no statistically significant difference between Mild, Moderate and Severe isolated GHD, p-value=0.6 regarding Z-score of initial height at time of diagnosis and p-value=0.74 regarding the height velocity after the first year of GH treatment.

In Group B(≥6 − < 11 years) and Group C (≥ 11 years) also no statistically significant difference, Group B (p-value =0.53 for Z-score and 0.92 for height velocity) and Group C (p-value= 0.63 for Z-score and 0.53 for height velocity).

Also the severity of GHD was not associated with sex (p-value= 0.552), or residency(p-value= 0.765) .

The no difference in variable parameters between Mild, Moderate and Severe GHD in this study may be attributed to the this laboratory classification that categorized the cases into 3 classes.

There was a number of researches who have classified GH−deficient short children according to peak GH response (**Daniela F. Cardoso et al**[17], **Symeznska et al** [18], **Van den Brocck J et al** [19]. All of these 3 studies considered a peak GH response < 5 ng/ml as severe(s GHD) and 5 - 10 ng/ml as partial (p GHD) or called mild .
Daniela F. Cardoso et al showed that mild and severe behave similarly in response to GH therapy during the first year , the increase in the height was not different between children with peak GH < 5 ng/ml and those with 5-10 ng/ml.This is consistent with the present study, in contrast to **Van den Brocck J et al** showed that growth response in the short term (1- and 2- years) in pGHD was significantly lower than the response seen in children with sGHD.

Regarding height deficit, **Symeznska et al** showed that significantly greater deficit of height were observed in sGHD than pGHD ,this is inconsistent with the study.

Symeznska et al and **Daniela F. Cardoso et al** made insulin-like growth factor as an additional parameter for comparison.

Symeznska et al and **Van den Brocck J et al** have studied short children with GHD (partial and severe) and idiopathic short stature(ISS) in which stimulatory GH peak (10-20 ng/ml) , not only GHD patients that studied in the present study , and compared between sGHD, pGHD, and ISS according to variable parameters , to assess the response to the treatment.In both reserches, the results showed this classical distinction of short stature groups that based on stimulated GH value is artificial and there is a need to use another ways of qualifying short children for GH therapy other than GH challenge test.

Conclusion:-

No significance of classification of short stature children with isolated GHD according to stimulated peak GH value with cut-off less 10 ng/ml.

References:-

1. [Guideline] Cohen P, Rogol AD, Deal CL, et al. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Pediatric Endocrinology Workshop. **J Clin Endocrinal Metab**. 2008 Nov. 93(11):4210-7.
2. Nwosu BU, Lee MM. Evaluation of short and tall stature in children. Am Fam Physician. 2008;78(5):597–604.
3. Lee, P.A., et. al. . Persistent short stature, other outcomes, and the effect of growth hormone treatment in children who are born small for gestational age . 2005 , 112(1), 150-162
4. Rose, S.R., et. al.. A general pediatric approach to evaluating a short child. Pediatrics in Review, 2005 , 26(11), 410-420
5. Lin-Su K,Wajnrajch MP.Growth hormone releasing hormone (GHRH) and GHRH receptor.2002.Rev Endocr Metab Disord.3(4):313-314
6. Gardner DG,Shoback .Greenspans Basic and Clinical Endocrinology .2007.pp.193-201
7. Yi S, Bernat B, Pál G, Kossiakoff A, Li WH .Functional promiscuity of squirrel monkey growth hormone receptor toward both primate and nonprimate growth hormones .2002, Mol.Biol.Evol. 19 (7):108392.
8. Bartholomew EF, Martini F, Nath JL . Fundamentals of anatomy & physiology. Upper Saddle River,2009, NJ: Pearson Education Inc. pp. 616–617
9. Nindl BC, Hymer WC, Deaver DR, Kraemer WJ. Growth hormone pulsatility profile characteristics following acute heavy resistance exercise .2001, J. Appl. Physiol. 91 (1): 163–72.
10. Mullis, P E. Genetic control of growth. Eur. J. Endocrinol .2005 , 152, 11-31 29- Growth Hormone Deficiency . UK Child Growth Foundation. 2009-01-16.
11. Hanew K, Utsumi AEur .The role of endogenous GHRH in arginine-, insulin-, clonidine- and L-dopa-induced GH release in normal subjects. J Endocrinol. 2002 Feb; 146(2):197-202.
12. Hilczer M, Smyczynska J, Lewinski A. Limitations of clinical utility of growth hormone stimulating tests in diagnosing children with short stature. Endocr Regul. 2006;40:69–75.
13. Cooke DW, Divall SA, Radovick S. Normal and aberrant growth in children. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. **Williams Textbook of Endocrinology**. 2016, 13th ed. Philadelphia, PA: Elsevier Saunders; :chap 24
14. Keane V. Assessment of growth. In: Kliegman R, Nelson WE, eds. Nelson Textbook of Pediatrics. 19th ed. Philadelphia, Pa.: Elsevier/Saunders; 2011.
15. Saggese G, Ranke MB, Saenger P, Rosenfeld RG, Tanaka T, et al. Diagnosis and treatment of growth hormone deficiency in children and adolescents; 1998, towards a consensus. Horm Res. 50:320–340
16. Gary Butler. Indications for growth hormone therapy. Paediatrics and Child Health 2007; 17: 9: 356-61.
17. Daniela F. Cardoso , Carlos Eduardo Martinelli Jr. et al. Comparison between the growth response to growth hormone (GH) therapy in children with partial GH insensitivity or mild GH deficiency.2014 Arq Bras Endocrinol Metab vol.58 no.1 São Paulo Feb.
18. Smyczyńska J[1], Lewiński A, Hilczer M, Stawerska R, Karasek M. Partial growth hormone deficiency (GHD) in children has more similarities to idiopathic short stature than to severe GHD. Endokrynol Pol. 2007 May-Jun;58(3):182-7.
19. Broeck Van den J, Arends N, Hokken-Koelega A: Growth response to recombinant human growth hormone (GH) in children with idiopathic growth retardation by level of maximum GH peak during GH stimulation tests. 2000, Horm Res. 53: 267-273.