Assessment of Quality of Life in a Sample of Short Stature Iraqi Children with Growth Hormone Deficiency

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Abstract:

Background: Short stature (SS) is defined as a height of 2.0 or more standard deviations (SD) below the population-specific mean height for age and gender. 2.5% of children have short stature, and it is one of the most frequent causes for children to see a growth specialist during their childhood. It is challenging to generalize about the effect of short stature on psycho-social adaption given the data currently available. Health-related quality of life (HrQoL) was generally shown to be lower in clinically identified short stature children than in population-based normal-sized reference groups.

Aim: Examine the behavioral pattern and mental health of SS and its psychological influence on QoL of children/adolescence. In addition, compare the behavioral response and QoL between growth hormone deficiency GHD and control groups.

Methods: It is a cross sectional study, included 80 participants (60 with GHD and 20 with normal height as control group) between 4 and 18 years old. The parents of the participants were given a parent-reported version of the written Quality of Life in Short Stature Youth QoLISSY questionnaire in Arabic in order to examine the association with the socio-demographic characteristics of the participants.

Results: 51.25% female and 48.75% male included in this study, the mean age at assessment was 12.1 ± 2.7, and 11.8 ± 2.6 of the GHD and control group, respectively. There was significant difference in QoLISSY total score between GHD and control groups. The association between socio-demographic characteristics of the participants was significantly different.

Conclusion: The QoL of Iraqi children with GHD showed lower scores in all domains of QoLISSY compared to normal children.

Keywords: Growth Hormone Deficiency, Quality of Life in Short Stature Youth Questionnaire, Short Stature Psychosocial Adaptation.

تقييم جودة الحياة في قصر القامة في عينة من الاطفال العراقيين المصابين بنقص هرمون النمو

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الخلاصة:

الخلفية: يُعرَّف قصر القامة على أنه ارتفاع ٢,٠ أو أكثر من الانحرافات المعيارية (SD) تحت متوسط الطول الخاص بالسكان بالنسبة للعمر والجنس. ٢,٥ ٪ من الأطفال لديهم قصر قامة، وهو أحد الأسباب الأكثر شيوعًا لرؤية الأطفال أخصائي النمو خلال طفولتهم. من الصعب التعميم حول تأثيرقصر القامة على التكيف النفسي والاجتماعي بالنظر إلى البيانات المتاحة حاليًا. أظهرت جودة الحياة المتعلقة بالصحة (HrQoL) عمومًا أنها أقل في الأطفال قصيري القامة الذين تم تحديدهم سريريًا مقارنةً بالمجموعات المرجعية ذات الحجم الطبيعي المستندة إلى السكان.

الهدف: فحص النمط السلوكي والصحة العقلية لـ قصر القامة وتأثيرها النفسي على جودة الحياة في اللأطفال / المراهقين. تحديد أوجه التشابه والاختلاف في الاستجابة السلوكية وجودة الحياة بين مجموعه نقص هرمون النمو ومجموعه التحكم.

طرائق العمل: هي دراسة مقطعية، شملت ٨٠ مشاركًا (٦٠ مشاركًا مع نقص هرمون النمو و٢٠ مشاركا بارتفاع طبيعي) تتراوح أعمارهم بين ٤ و١٨ عامًا. تم إعطاء أولياء أمور المشاركين نسخة من استبيان جودة الحياة في قصر القامه QoLISSY المكتوب باللغة العربية من أجل فحص الارتباط بالخصائص الاجتماعية والديموغرافية للمشاركين.

النتائج: اشتملت الدراسة على ٤٨,٧٥٪ ذكور و٥١,٢٥٪ إناث. كان متوسط العمر عند التقييم ١٢,١ ± ٢,٧، و١١,٨ ± ٢,٦ لمجموعة نقص هرمون النمو ومجموعة التحكم، على التوالي. كان هناك فرق كبير في مجموع نقاطQoLISSY بين مجموعه نقص هرمون النمو ومجموعاة التحكم. كان الارتباط بين الخصائص الاجتماعية والديموغرافية للمشاركين فرقًا كبيرًا.

الاستنتاج: أظهرت جودة الحياة للأطفال العراقيين المصابين بـنقص هرمون النمو درجات أقل في جميع مجالات QoLISSY مقارنة بالأطفال العاديين.

الكلمات المفتاحية: نقص هرمون النمو، استبيان جودة الحياة في قصر القامة للشباب، التكيف النفسي الاجتماعي لدى قصير القامة.

Introduction

Short stature (SS) is defined as a height of 2.0 or more standard deviations (SD) below the population-specific mean height for age and gender [1]. 2.5% of children have SS [2]. The biological mother's and father's average heights serve as the foundation for the anticipated height (goal height). Thus, a person of a certain height in cm may be regarded as having SS in one nation but not in another [3]. According to the survey done by Sadiq, et al. (2022) in Kirkuk, 97% of young adolescent parents are unaware that their child's shortness is caused by illnesses and wrongly think it is due to a delay in the child's growth or inherited factors [4]. The incidence of growth hormone deficiency (GHD) in pediatric patients with SS in Al-Hassan Centre of Endocrinology and Diabetes in Karbala Province was 1/2500 of total target population with male to female gender predilection 1.3/1 [5]. SS classified into primary growth failure, secondary growth failure, and idiopathic short stature, each with multiple subcategories [6]. GHD, Familial Short Stature (FSS), and Constitutional Delay in Growth and Puberty (CDGP) were the leading causes of SS in Iraqi patients referred to hospitals [7]. Growth hormone GH is a 191 amino acid protein (molecular weight of 22 kDa) produced and released in a pulsatile fashion from the anterior pituitary under positive control of GH-releasing hormone and negative control of somatostatin, both produced by the hypothalamus [8]. GH influences the release of both glucose and IGF-1 from the liver, as well as the content of fatty acids in adipose tissue [9]. The most typical symptom of GHD is growth failure, which often manifests in infancy and early childhood. The bone age will normally be delayed, and the height percentile of a child with GHD will gradually drop [10]. For the diagnosis of SS, biochemical and radiographic studies are required, as well as assessments of nutritional status,

hormonal status, and bone age [10]. Of note, in children with GHD, GH therapy is frequently utilized since it can speed up growth, enhance final height, and improve metabolism [11]. According to recent studies, GH therapy not only promotes normal growth but also improves defective lipid and amino acid metabolic conditions [12]. A final adult height within the genetic target range determined by parental heights is the main goal of treatment. Daily subcutaneous injection of GH is given in the evening [13]and the significant inter-individual variations in SS adaptation and the effects of being short may be influenced by a number of risk and protective factors, including parental attitudes and prevailing cultural beliefs [14]. The importance of adaptation, the potential effects of stature height, and the effects of GH therapy need to be researched in order to better understand psychological functioning [15]. SS children and adolescents are more prone to experience isolation and discrimination because they are regularly teased, rejected, or overprotected by peers, teachers, and parents, in addition to facing environmental obstacles to the development of autonomy [16]. Health related Quality of Life (HrQoL) has been introduced as a multidimensional health indicator[17,18], covering the physical, emotional, and social aspects of well-being and functioning [19]. HrQoL was generally shown to be lower in clinically identified SS children than in population-based normal-sized reference groups. The Quality of Life in Short Stature Youth (QoLISSY) questionnaire was specifically developed to assess QoL in children with SS from the viewpoints of both the patient and the parents [19]. Routine assessment of HrQoL in pediatric healthcare may help identify children for referral to specialized psychological assessment and intervention [15].

This study designed to examine the behavioral pattern and mental health of SS and its psychological influence on QOL of children/adolescence. In addition, compare the behavioral response and QoL between growth hormone deficiency and control groups.

Methods

It is a cross sectional study, included 80 participants (60 with GHD and 20 with normal height as control group) between 4 and 18 years old[20]. The parents of the participants also involved in this study. All 60 diseased patients were previously diagnosed at the Central Teaching Hospital of Pediatrics and are being administered rhGH treatment continuously for not less than 6 months as follow-up [21]. Participation and data collection started in the middle of September 2022 and continued until the end of December 2022. The exclusion criteria included patient with chronic systemic diseases and severe mental disorders and/or other chronic health conditions that would potentially lower the QoL by other means than height along with low cognitive ability to understand and complete the questionnaires by the parents [22]. According to the inclusion criteria, the control group was randomly collected from outside the hospital, and they are healthy, of normal height, and within the age range of 4 to 18 years old. The socio-demographic (age, gender, BMI, BMI%, duration of disease, co-existing diseases, family history, number of children affected, residence, monthly income , and educational level) and clinical data of the participants were collected along with the laboratory investigation which included serum GH and IGF-1 level. In this study, a clonidine stimulation test was used to obtain the level of GH for confirmation of the diagnosis after suspicion of the presence of GHD according to certain criteria [23]. The clinical assessment of the participants included the administration of the parent reported version of written QoLiSSY questionnaire in Arabic to assess their QoL. The QoLISSY Questionnaire for parents consists of 22 Likert-scaled items assigned to three core dimensions:

Physical, Social, Emotional, and the 44 additional items in the dimensions: Coping, Beliefs and Treatment (reflecting child assessment) as well as Future and Effect on parents [24]. All items were answered using a standard 5-point Likert scale ranging from 1 (not at all/never) to 5 (extremely/always), providing standardized scores (0–100) for each scale and for a total HrQoL score, representing the mean of the three core domains. Higher values on sub-scales or general scores indicate better quality of life for each of the QoLISSY modules. A P-value less than 0.05 were considered statistically significant. R software packages (dplyr, gtsummery and ggplot) were used for data processing, visualization, and statistical analysis ("R version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria"). This research was approved by the Chairman of the Research Ethics Committee of Almustansiriyah University/College of Pharmacy.

Results

The study included 80 participants, with 51.25% female and 48.75% male. The mean age at assessment was 12.1 ± 2.7 and 11.8 ± 2.6 of the GHD and control group, respectively. No significant difference regarding age and gender in the GHD and control groups, but there was significant difference regarding BMI, BMI percentile, and BMI percentile classification (p-value 0.023, 0.013, and 0.032, respectively). The majority of participants were with normal BMI percentile ranging from ≥5% to <85%. There was 16.7% of GHD underweight compared to 5% of control group. The mean duration of disease in months for the GHD was 24.6 ± 23.8. Two third of GHD had the disease for ≤ 24 months. Only 6.7 % have co-existing diseases among GHD group (ex. Epilepsy, heart defect, and other). GHD patients had a 28.3% family history of SS, with 1-4 children diagnosed with SS in the same family. The residence of participants showed a significant difference (*p*-value < 0.001). Also, there was a significant difference regarding the monthly income of the families (*p*-value < 0.001). Regarding the educational level of the participants, about 95% of them were in primary and secondary school, with no significant differences between them. Table (1) below describes the socio-demographic characteristics of the participants.

Table 1: Description of the Socio-Demographic Characteristics of the Participants

Characteristics	GHD, N=60[1]	Control, N=20[1]	P-value[2]
Age, years	12.1 ± 2.7	11.8 ± 2.6	0.7
4-7	5 (8.3%)	1 (5.0%)	0.14
8-12	21 (35.0%)	12 (60.0%)	
13-18	34 (56.7%)	7 (35.0%)	
Gender			
Male	29 (48.3%)	10 (50.0%)	>0.9
Female	31 (51.7%)	10 (50.0%)	
BMI (kg/m^2)	17.6 ± 2.7	19.9 ± 3.8	**0.023**
BMI percentile	41.6 ± 32.2	64.2 ± 33.3	**0.013**
< 5	10 (16.7%)	1 (5.0%)	**0.032**
≥ 5 to <85	43 (71.7%)	11 (55.0%)	
≥ 85 to < 95	4 (6.7%)	5 (25.0%)	
≥ 95	3 (5.0%)	3 (15.0%)	
Duration of disease (months)	24.6 ± 23.8		
<12 months	21 (35.0%)		

12-24 months	21 (35.0%)		
>24 month	18 (30.0%)		
Co-existing disease	4 (6.7%)		
Family history	17 (28.3%)		
No. of children affected	1 (1-4)		
Residency			
Rural area	49 (81.7%)	0 (0.0%)	**<0.001**
Urban area	11 (18.3%)	20 (100.0%)	
Monthly income (IQD million)			
<0.5	43 (71.7%)	0 (0.0%)	**<0.001**
0.5-1	13 (21.7%)	13 (65.0%)	
>1	4 (6.7%)	7 (35.0%)	
Educational level			
pre school	2 (3.3%)	1 (5.0%)	0.7
Primary-school	26 (43.3%)	11 (55.0%)	
Secondary- school	31 (51.7%)	9 (45.0%)	
No school	3 (5.0%)	0 (0.0%)	

[1]Mean ± SD; n (%)
[2]Welch Two Sample t-test; Pearson's Chi-squared test; Fisher's exact text

The mean duration of treatment in months for the GHD group was 14.7 ± 8.9. The means of serum GH and IGF-1 levels in ng/ml were 3.9 ± 2.0 and 158.7 ± 84.6, respectively. The mean height in cm of the GHD group before and after continuous treatment was 127.2 ± 15.3 and 136.9 ± 16.0, respectively, Table (2).

Table 2: Description of the Clinical Characteristics of GHD group

Characteristics		GHD, N=60[1]	
Duration of treatment (months)		14.7 ± 8.9	
<12 months		25 (41.7%)	
12-24 months		32 (53.3%)	
>24 months		3 (5.0%)	
Serum GH (ng/ml)		3.9 ± 2.0	
Serum IGF-1 level (ng/ml)		158.7 ± 84.6	
Height (cm)			
Pre-treatment		127.2 ± 15.3	
Post-treatment		136.9 ± 16.0	

[1]Mean ± SD; n (%)

Regarding the QoL of participants, the control group showed significantly higher scores in the physical, social, and emotional domains with a *p*-value less than 0.001 while the GHD group have showen lower scores in these three domains as shown in Table (3). The QoLISSY total score for groups was significantly different, with a *P*-value less than 0.001.

Table 3: Quality of Life in Short Stature Youth (QoLISSY) Questionnaire

Characteristics		GHD, N=60[1]	Control, N=20[1]	P-value[2]
Physical		77.4 ± 22.3	99.0 ± 3.3	**<0.001**
Social		67.8 ± 24.0	97.5 ± 20.4	**<0.001**
Emotional		64.8 ± 24.1	91.7 ± 6.9	**<0.001**
QoLISSY total score*		70.0 ± 21.6	96.1 ± 8.4	**<0.001**
Coping		49.9 ± 11.9		
Height related believes		43.5 ± 21.1		
Treatment experiences		59.0 ± 9.1		
Future concern		61.8 ± 24.7		
Effects on parents		56.5 ± 21.8		

[1]Mean ± SD
[2]Welch Two Sample t-test
*QoLISSY total score is sum of physical, social and emotional domains.

The age at assessment of the participants showed significant differences in the age classifications of the groups in comparison with the total QoLISSY score, with a *p*-value less than 0.001, while there were no significant differences regarding each group's classification separately. There was significant difference in BMI % between groups when compared to total QoLISSY score. The gender of the two groups showed a significant difference when compared with the total QoLISSY score, with a *p*-value less than 0.001. The GHD group showed a significant difference in total QoLISSY score between male and female, with a *p*-value of 0.047. The residency area, the monthly income, and the educational level of the groups showed significant differences when compared with the total QoLISSY score, while no significant differences occurred among the classifications in the groups separately, Table (4).

Table 4: Association of Patient's Demographic Characteristics with Total QoLISSY Scores of GHD and Control Groups

Parameters		Total QoLISSY score		
		GHD[1]	**Control[1]**	***P*-value[2]**
Age at assessment (years)	4-7	89.8 ± 6.9	94.8 ± NA	NA
	8-12	65.4 ± 24.6	95.6 ± 10.9	**<0.001**
	13-18	69.9 ± 19.8	97.0 ± 2.3	**<0.001**
***P*-value[2]**		0.074	>0.9	
BMI%	<5%	61.6 ± 23.2	91.7 ± NA	NA
	≥5%-<85%	71.9 ± 21.1	98.2 ± 8.9	**<0.001**
	≥85%-<95%	64.4 ± 31.6	93.7 ± 10.1	0.15
	≥95%	77.3 ± 4.1	93.5 ± 4.5	**0.01**
***P*-value[2]**		0.5	0.7	
Gender	Male	64.2 ± 22.4	96.5 ± 11.9	**<0.001**
	Female	75.3 ± 19.8	95.6 ± 2.8	**<0.001**
***P*-value[2]**		**0.047**	0.8	
Residency area	Rural	69.1 ± 21.2	NA ± NA	NA
	Urban	73.9 ± 24.3	96.1 ± 8.4	**0.01**
***P*-value[2]**		0.6		
Monthly income (Million IQD)	<0.5	71.1 ± 21.7	NA ± NA	NA
	0.5-1	71.0 ± 19.7	94.4 ± 2.8	**0.001**
	>1	54.3 ± 26.5	99.1 ± 13.9	**0.035**
***P*-value[2]**		0.3	0.4	
Educational level	Pre-school	94.1± 3.4	94.8± NA	NA
	Primary school	70.7 ± 24.6	97.9 ± 9.8	**<0.001**
	secondary school	69.8 ± 18.4	94.2 ± 7.2	**<0.001**
	No school	65.5 ± 34.0	NA ± NA	NA
***P*-value[2]**		0.5	0.7	

[1]QoLISSY total score: Mean ± SD
[2]One-way ANOVA; Welch Two Sample t-test

The total QoLISSY score showed a negative correlation with the duration of continuous treatment, as shown in Table (5), with a *p*-value of 0.012, indicating a significant difference between them, while a positive correlation with height change.

Table 5: Correlation between Clinical Parameters and Total QoLISSY Scores of GHD Group

Characteristics	QoLISSY (R)*	*P*-value
Duration of treatment (months)	-0.24	**0.012**
Height change	0.11	0.26
*Pearson's product-moment correlation		

Discussion

The main objective of this cross-sectional study was the assessment of the QoL in a sample of Iraqi children and adolescents with diagnosis of GHD and it is the first study performed in Iraq (exploratory end point). Regarding the demographic characteristics of the SS group and the control group, no significant difference was found in age or gender distribution between them. This result matches that of Toshiaki, et al. (2021) who shows the percentage of children diagnosed with GHD did not differ significantly between boys and girls [25]. The control group has significantly higher BMI than the SS group. The majority of participants were with normal BMI percentile. However, 16.7% of the GHD group was underweight compared to 5% of the control group. Reinehr, et al. (2014) shows that obese children at the onset of GH treatment decreased their BMI-SDS, while underweight and normal weight children at the onset of GH treatment increased their BMI-SDS independently of GH treatment indication, therefore, GHD patients showed an increase in their weight with treatment [26]. There was a significant difference regarding the residency of the participants, with the majority of the SS group living in rural areas compared to the control group, which lives in urban areas. Also, there was a significant difference regarding the monthly income of the groups, with the majority of the SS group having a monthly income less than 0.5 million IQD while the majority of the control group have a monthly income between 0.5 and 1 million IQD. Those last findings suggest the influence of residency and economic state on the development of GHD. The educational level of the participants was similar with the majority of participants being in the primary and secondary school. The parents of SS children, compared to the parents of children with normal height, reported that their children are less socially competent and in general have more social problems [27]. The result of this study shows the impact of SS on QoL in children compared to the control group, with a significant difference regarding the mean total score of the groups (a p-value of < 0.001), which includes physical, social, and emotional domains. The children reported having more emotional problems than social and physical problems, as indicated by the lower score in the emotional domain that affects QoL. The additional domains regarding height-related beliefs, treatment experiences, future concerns and effect on parents were also depressed among SS group. The controls with normal stature had significantly better QoL and cognitive function than children with GHD [28]. The height as a continuous variable was a significant predictor of QoL overall [29]. There was no significant relationship observed between the patient's demographic data and the total QoLISSY scores in GHD group, except in the gender, in which males reported less QoL than females and it was significantly different. This study shows the contribution of male gender, age between 8 and 12 years old, normal and obese BMI%, with urban residency, moderate to high monthly income, and within primary to secondary school to the lowest QoL between the GHD and control group. It is important to keep in mind that emotional problems that appear during childhood, linked to chronic conditions, may persist beyond childhood into adult life [30]. This observation suggests it is important to address SS during childhood, as early as possible, to minimize the impact on future QoL. The correlation in this study shows the significant difference in the duration of continuous treatment, in which the QoLISSY total score was decreased when the duration of treatment increased, indicating decreased QoL. This is due to the fact that an increasing duration of treatment means that the child does not reach his target height fast and has a low response to treatment, therefore increasing the duration of the disease and the psycho-

social problems in both patients and their families. However, a study done by González Briceño, et al. (2019) and Quitmann, et al. (2019) shows that there was a significant improvement in the physical, social, and emotional domains of the parents reported version of the QoLISSY questionnaire after 1 year of GH treatment [31,32]. The increasing duration of treatment in Iraq was not just because of the low response to treatment but also due to the unavailability of GH pens and the difficulty of parents in providing these pens to their children due to the cost, resulting in treatment interruption and less improvement in height gain.

Conclusion

The QoL assessment of Iraqi children with GHD showed lower scores in all domains of QoLISSY compared to normal children, indicating the influence of short stature on psychological behavior and QoL.

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