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Assessment of health-related quality of life in Egyptian children and adolescents with congenital adrenal hyperplasia

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Abstract

Background: Congenital adrenal hyperplasia (CAH) is a chronic disorder causing adrenal insufficiency and hyperandrogenism affecting the quality of life (QOL). The objective of the study was to assess the health-related QOL (HRQOL) in Egyptian children and adolescents with CAH and to identify factors affecting it.

Methods: This cross-sectional study included 200 CAH patients (with 21-hydroxylase deficiency [21-OHD]) who were assessed according to their age, sex, clinical phenotype, timing of genitoplasty, hospital admissions within the last year, compliance to treatment, regularity of follow-up, presence of complications and hormonal control. HRQOL was assessed using the World Health Organization (WHO)QOL-BREF questionnaire with four domains analyzed independently including physical, psychological, social and environmental domains, with higher scores indicating better QOL.

Results: The study included 140 females and 60 males with a mean age of 6.6 ± 4.5 years, and 88% were salt-wasting (SW). Older patients had significantly lower QOL scores ($r = -0.151$, $p = 0.033$). The physical domain correlated significantly with the degree of virilization ($r = -0.491$, $p = 0.001$) and frequency of hospitalization ($r = -0.495$, $p < 0.001$). The psychological domain was affected by age ($r = -0.157$, $p = 0.026$) and timing of genitoplasty ($r = -0.326$, $p = 0.001$), while the social domain was affected by age ($r = -0.277$, $p < 0.005$) and pubertal stage ($r = -0.195$, $p = 0.006$). Females had lower scores at the psychological domain ($p < 0.001$), whereas males had lower scores at the physical domain ($p = 0.003$). Salt-losing patients had lower scores at the physical domain ($p = 0.001$). Patients with good hormonal control had higher scores at the physical domain ($p = 0.03$). Genitoplasty affected both psychological and social domains ($p = 0.003$ and 0.01, respectively). Patients with hypertension and hirsutism had lower QOL scores ($p < 0.05$).

Conclusions: HRQOL was relatively more affected in CAH patients with older age, poor hormonal control, high frequency of hospital admissions and those who developed complications.

Keywords: 21-hydroxylase deficiency; congenital adrenal hyperplasia; genitoplasty; hormonal control; quality of life; WHOQOL-BREF questionnaire.

Introduction

In recent decades, the progress in medical treatment of several chronic disorders has led to increased survival rates with shifting the focus toward quality of life (QOL) [1]. QOL is a multi-dimensional concept involving different domains such as physical health, psychological well-being, social relationships, economic circumstances, personal beliefs and their relation to other environmental features. Health-related QOL (HRQOL) refers to the "patient's sense of his own health and well-being in the broad areas of physical, psychological and social functioning" [2].

Congenital adrenal hyperplasia (CAH) is an inherited autosomal recessive disorder characterized by impaired cortisol synthesis with subsequent hyperplasia of the adrenal gland due to loss of negative feedback mechanism with activation of the hypothalamic pituitary adrenal axis [3, 4]. Steroid 21-hydroxylase deficiency (21-OHD) caused by mutations in the *CYP21A2* gene encoding the adrenal 21-hydroxylase, P450c21, represents more than 95% of CAH cases [5, 6]. CAH patients can be salt-wasting (SW), simple virilizing (SV) or non-classic (NC) that may be asymptomatic or associated with signs of postnatal or even adult-onset androgen excess [7, 8].

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Replacement therapy in CAH aims to correct corticosteroid and mineralocorticoid deficiencies and to normalize hyperandrogenism to improve normal life expectancy and HRQOL. However, throughout the disease course, many problems can be encountered including disturbed pubertal development, reduced final height, adrenal crisis during childhood, and multiple hormonal and metabolic long-term consequences such as decreased bone mineral density, obesity and altered reproductive function in adulthood, which might have a significant impact on HRQOL [9]. Recent studies have shown a reduction in QOL in CAH patients being more often single, less sexually active, and displaying a negative body image with less self-confidence, sociability and social acceptance [10, 11]. Several factors can affect QOL in CAH patients such as genital ambiguity necessitating surgery, impaired growth with short final adult height, hirsutism, hypertension, repeated adrenal crisis, overweight and metabolic syndrome [8, 12]. The aim of the current study was to assess the HRQOL in Egyptian children and adolescents with CAH and identify the factors affecting it.

Methodology

Study design

This cross-sectional study included 200 CAH children and adolescents (with 21-OHD) of both sexes between 1 and 18 years of age following up regularly at the Diabetes, Endocrine and Metabolism Pediatric Unit (DEMPU), Cairo University for at least 6 months. Diagnosis of 21-OHD was based on clinical and laboratory data (elevated 17-hydroxyprogesterone [17-OHP]) as well as molecular studies. CYP21 mutations revealed I2Splice in 52.6% cases followed by P30L, Del 8bp E3, Q318X, V281L, L307 frameshift, Cluster E6 and P453S. Informed consents were taken from patients and their legal guardians before completing the questionnaire.

Methodology

The study group was subjected to detailed history-taking including the age, sex of rearing and sex of reassignment, consanguinity, presence of similar conditions in the family, age of onset, type of CAH (SW, SV or NC), type and age of genitoplasty, frequency of hospital admissions within the last year, medications (type and dose), compliance to treatment, regularity of follow-up, and presence of complications (precocious puberty, hypertension, growth failure or complications related to genitoplasty).

A thorough clinical assessment was performed including anthropometry (weight and weight standard deviation score [SDS], height and height SDS, body mass index [BMI] and BMI SDS, previous year height velocity, previous year height velocity SDS), blood pressure (BP) measurement (readings plotted on Egyptian BP charts), presence of pigmentation, pubertal staging using Tanner stage [13] and presence of hirsutism (using the Ferriman-Gallwey score) in addition to full genital examination. The Prader score was used to assess the degree of virilization in females [14].

Levels of 17-OHP as well as other adrenal precursors (testosterone and androstenedione) were obtained from patients' medical records and their mean values within the last year were calculated. Monitoring of therapy was assessed via clinical and biochemical parameters. Cases were considered to be well controlled in the absence of excessive skin pigmentation, advanced growth velocity, hirsutism or precocious puberty with no elevation in 17-OHP, adrenal androgens or plasma renin activity.

Questionnaire

The WHOQOL-BREF questionnaire used in our study consisted of 26 items assessing four main domains (physical health, psychological health, social relationships and environmental domain) that cover the aspects proposed to judge QOL. One item about appreciation of sex life (question number 21), present in the social domain, was discarded from the questionnaire taking into consideration the young age of the patients of the study group as well as the social stigmata in the study population. In 82 (41%) of our patients, the WHOQOL questionnaires were administered to patients themselves as they had enough reading ability, while in younger patients (59%), we interviewed them with the help of the available parent attending with the child. The investigator herself explained each question.

Scores were scaled in a positive direction, with higher scores denoting higher QOL. Each item was scored on a five-point Likert scale (1–5) and a mean score calculated for each domain. The mean score was subsequently transformed into a 0–100 scale score, directly comparable to the WHOQOL-100. Scoring, checking data and computing domain scores were done according to instructions in the WHOQOL-BREF manual (annex 3) (WHOQOL Manual-Body.doc, 2005).

Statistical analysis

All collected questionnaires were revised for completeness and accuracy. Data were coded and tabulated on a computer for analysis. An Excel database was developed for data entry. Data were analyzed using the Microsoft Excel program version 2007 (Microsoft Corp., Redmond, WA, USA) and SPSS program for windows version 21 (IBM Corp., Armonk, NY, USA). Quantitative data were presented as frequencies and percentage. After checking for data normality, descriptive statistics in the form of arithmetic mean and standard deviation were used to summarize quantitative normally distributed data, while median with minimum and maximum were used to describe non-normally distributed data. Independent samples Student's t test was used to compare scores between groups. A p-value less than 0.05 was considered significant. Spearman's rho correlation was done to assess the correlation between different quantitative variables and different domains of WHOQOL.

Results

Descriptive data of the study group

The current study included 140 females and 60 males with a mean age of 6.6 ± 4.5 years, and 88% (n = 176) were SW, 11% (n = 22) were SV and 1% (n = 2) were NC CAH.

In our cohort, 137 (68.5%) children were initially reared as males and 63 (31.5%) were reared as females but after karyotyping and final diagnosis, 140 (70%) were finally reared as females and 60 (30%) were finally reared as males (i.e. 77 (56.2%) males were reassigned as females after diagnosis). Regarding genital surgery, 97 (69.3%) females had undergone clitoroplasty between 0.41 and 8 years with a mean age of 2.1 ± 1.3 years, and six females (4.3%) had vaginoplasty after clitoroplasty at a mean age of 7.1 ± 3 years. Regarding development of complications among the study group, 19 (9.5%) had precocious puberty, 11 (5.5%) had hypertension, 18 (12.8%) females developed hirsutism, the final adult height was <– 2 SDS (short stature) in six (50%) patients, four (2%) females had urinary incontinence after genitoplasty, three (5%) boys developed testicular adrenal rest tumors (TART) and only one female (0.7%) had polycystic ovary syndrome (PCOS) (Tables 1 and 2).

Table 1: Characteristics of the study group (a).

	No.	%
Initial sex of rearing		
Male	137	68.5
Female	63	31.5
Sex of reassignment		
Male	60	30.0
Female	140	70.0
Type of CAH		
Salt-wasting	176	88.0
Simple virilizing	22	11.0
Late onset	2	1.0
Presence of complications		
Precocious puberty	19	9.5
Hirsutism	18	12.8
Hypertension	11	5.5
Short adult stature	6	50
Pigmentations	45	22.5
Urinary incontinence	4	2
TART	3	5
PCO	1	0.7
Surgical correction		
Done		
Clitoroplasty	97	69.3
Vaginoplasty	6	4.3
Not done yet	43	30.7

CAH, congenital adrenal hyperplasia; PCO, polycystic ovary; TART, testicular adrenal rest tumor.

Assessment of QOL in the study group

The current study showed an overall decrease in HRQOL in children and adolescents with CAH. The psychological and social domains showed lower scores than the physical and environmental domains with a mean total QOL score of 314.6 ± 26 (Figure 1).

Correlation between total scores of WHOQOL and different variables showed that QOL was affected by the patients' age (older children and adolescents had lower QOL total scores), Prader score in females (i.e. degree of

Table 2: Characteristics of study group (b).

	Mean ± SD	Median	Min	Max
Age, years	6.6798 ± 4.54	5.2050	1.00	18.00
Age at diagnosis, days	48.05 ± 273.89	4.00	0	3600
Weight SDS	−0.1435 ± 1.88	−0.6500	−4.10	6.40
Height SDS	−0.8745 ± 1.44	−1.0000	−4.50	3.80
BMI SDS	0.9095 ± 1.33	0.8500	−3.00	3.90
Previous year ht velocity SDS	0.3200 ± 1.93	0.4000	−4.20	4.80
Systolic blood pressure	104.31 ± 14.97	103.00	79	154
Diastolic blood pressure	69.07 ± 10.58	67.00	47	112
Dose of glucocorticoids, mg/m²/day	16.7415 ± 4.43	16.6000	6.70	36.00
Frequency of glucocorticoids (number of doses/day)	3.0 ± 0.0	3.00	2	4
Dose of mineralocorticoids, mg/day	0.0788 ± 0.07	0.0500	0.03	0.75
Age of clitoroplasty	2.1193 ± 1.40	2.0000	0.41	8.00
Age of vaginoplasty	7.1667 ± 3.06	7.0000	4.00	12.00

BMI, body mass index; SD, standard deviation; SDS, standard deviation score.

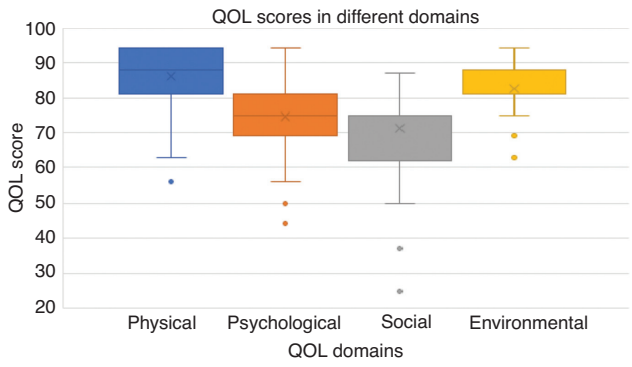

Figure 1: Mean scores in different WHOQOL domains (total score of each domain = 100).

virilization), frequency of hospital admissions in the previous year, dose of mineralocorticoids and level of androgens (androstenedione). However, it was not affected by the age at diagnosis of CAH or age of genitoplasty (Table 3). Correlation between the physical domain of WHOQOL and different variables showed that females with a higher Prader score as well as those with a history of increased number of hospital admissions within the previous year showed statistically significant lower scores. Older patients, females who had undergone clitoroplasty at an older age, those on higher doses of mineralocorticoids and those with higher levels of androstenedione had significantly lower scores regarding the psychological domain of the WHOQOL. The social domain was more affected in older as well as more pubertal patients, while the environmental domain was affected by the frequency of hospital admissions.

Older children and adolescents showed lower QOL scores at the psychological and social domains as well as total scores (p = 0.026, <0.001 and 0.033, respectively). Females showed statistically significant lower scores at the psychological domain (p < 0.001), while males showed statistically significant lower scores at the physical domain (p = 0.003) (Table 4). SW CAH patients showed lower scores at the physical domain compared to SV patients (p = 0.001) (Table 4). Patients with positive consanguinity showed statistically significant lower scores at the social domain (p = 0.03). However, the presence of affected siblings in the same family did not affect QOL scores.

Females who had undergone genitoplasty showed statistically significant higher scores at the psychological domain compared to those who were not operated yet (p = 0.003). Regarding the timing of surgery in relation to QOL, we found that patients who had undergone clitoroplasty at an older age showed statistically significant lower QOL scores at the psychological domain (p = 0.001).

Table 3: Correlations between WHOQOL domains and different study parameters.

Study parameter	Physical domain		Psychological domain		Social domain		Environmental domain		Total QOL score	
	r	p-Value	r	p-Value	r	p-Value	r	p-Value	r	p-Value
Age, years	0.119	0.099	−0.157	**0.026**	−0.277	**<0.001**	−0.066	0.351	−0.151	**0.033**
Age at diagnosis, days	−0.03	0.669	0.044	0.535	0.012	0.866	−0.037	0.600	0.002	0.977
Age of clitoroplasty, years	−0.069	0.5	−0.326	**0.001**	−0.147	0.152	−0.007	0.947	−0.192	0.060
Age of vaginoplasty, years	−0.375	0.464	−0.079	0.881	−0.455	0.3650	−0.397	0.435	−0.403	0.428
Tanner staging	0.037	0.606	−0.063	0.377	−0.195	**0.006**	−0.072	0.311	−0.086	0.224
Prader score (in females only, n = 140)	−0.491	**0.001**	−0.100	0.522	−0.201	0.196	−0.213	0.171	−0.314	**0.041**
Number of hospital admissions in the last year	−0.495	**<0.001**	−0.019	0.7870	−0.043	0.544	−0.141	**0.047**	−0.272	**<0.001**
Dose of glucocorticoids, mg/m²/day	0.079	0.269	0.009	0.895	0.007	0.919	−0.072	0.308	0.015	0.835
Number of doses of glucocorticoids per day	−0.098	0.166	0.073	0.307	0.105	0.141	−0.103	0.145	−0.022	0.762
Dose of mineralocorticoids, mg/day	−0.072	0.324	−0.195	**0.007**	−0.141	**0.05**	−0.031	0.669	−0.154	**0.033**
Level of Δ4 androstenedione within the last year, ng/mL	−0.185	0.07	−0.288	**0.004**	−0.242	**0.017**	−0.084	0.411	−0.274	**0.007**
Level of testosterone within the last year, ng/mL	−0.303	**0.05**	−0.048	0.761	−0.122	0.441	−0.111	0.485	−0.172	0.277

Bold values are statistically significant.

Table 4: Comparing QOL scores in relation to different study parameters.

	Physical domain (100)		Psychological domain (100)		Social domain (100)		Environmental domain (100)		Total QOL score (400)	
	Mean score	**p-Value**	**Mean score**	**p-Value**	**Mean score**	**p-Value**	**Mean score**	**p-Value**	**Mean score**	**p-Value**
Final sex of rearing										
Males	83.62±8.87	**0.003**	79.20±5.16	**<0.001**	73.33±9.77	0.089	83.00±5.57	0.532	319.2±22.9	0.109
Females	87.31±7.60		72.59±9.04		70.35±11.92		82.44±5.84		312.7±27.2	
Clinical type of CAH[a]										
SW	85.53±8.21	**0.001**	74.53±8.48	0.853	70.77±11.45	0.275	82.49±5.74	0.590	313.3±26.3	0.149
SV	91.77±5.61		74.55±10.11		74.73±10.86		83.73±6.16		324.8±23.6	
NC	84.50±4.95		78.00±4.24		75.00±0.0		81.0±0.0		318.5±9.2	
Consanguinity										
+ve	86.26±8.24	0.887	74.09±8.44	0.268	70.01±12.2	**0.03**	82.59±5.81	0.956	312.9±26.9	0.282
–ve	86.09±8.1		75.52±8.9		73.7±9.14		82.64±5.7		317.9±24.2	
Positive family history										
Yes	86.25±8.5	0.967	75.77±8.9	0.237	71.55±12.9	0.822	83.42±6.5	0.236	316.9±29.7	0.445
No	86.19±8.1		74.14±8.5		71.14±10.79		82.32±5.46		313.8±24.7	
Compliance with treatment										
Yes	86.83±8.4	0.21	75.39±7.5	0.119	72.92±10.4	**0.016**	83.43±5.2	**0.02**	318.6±23.8	**0.013**
No	85.37±7.8		73.48±9.8		69.02±12.2		81.52±6.3		309.4±28	
On regular follow-up										
Yes	86.35±8.4	0.598	75.08±8.1	0.07	71.79±11.5	0.143	83.0±5.7	**0.037**	316.2±25.9	0.062
No	85.54±7.2		72.17±10.6		68.69±10.7		80.77±5.9		307.2±26.2	
Hormonal control (17-OHP)										
Well	86.51±8.46	**0.03**	74.7±8.55	0.692	71.67± 11.4	0.317	82.71±5.74	0.640	315.6±26.4	0.325
Poor	83.11± 6.93		74.11±8.95		69.73±11.3		82.25±5.86		311.2±24.9	
Clitoroplasty done										
Yes	87.57±7.6	0.556	74.07±10.1	**0.003**	69.55±12.9	0.232	82.26±5.9	0.575	313.4±29.9	0.625
No	86.74±7.7		69.23±4.8		72.16±8.9		82.86±5.8		311.0±19.8	
Vaginoplasty done										
Yes	83.33±6.7	0.191	68.83±6.9	0.301	58.17±15.3	**0.01**	82.33±4.9	0.936	292.7±26.66	0.065
No	87.49±7.6		72.75±9.1		70.90±11.5		82.45±5.9		313.6±26.9	

17-OHP, 17-hydroxyprogesterone; CAH, congenital adrenal hyperplasia; NC, non-classic; SV, simple virilizing; SW, salt-wasting. [a]p-Value is calculated between SW and SV types of CAH (as no. of late onset CAH was too small). Bold values are statistically significant.

Patients who were compliant with treatment showed statistically significant higher scores at the social and environmental domains, and total scores compared to non-compliant patients (p = 0.016, 0.02 and 0.013, respectively), while patients on regular follow-up had statistically significant higher scores at the environmental domain (p = 0.037). Patients receiving large doses of mineralocorticoids showed statistically significant lower QOL scores at the psychological and social domains as well as total scores of WHOQOL (p = 0.007 and 0.03). Well-controlled patients showed higher QOL scores than poor-controlled patients (p = 0.03) regarding the physical domain, while patients with high serum levels of androstenedione showed statistically significant lower scores at the psychological domain, social domain as well as total QOL score (p = 0.004, 0.017 and 0.007, respectively), and those

Table 5: Relation between the presence of different CAH complications and QOL.

WHOQOL domain	Complication	Present Mean score ± SD	Absent Mean score ± SD	p-Value
Physical domain (100)	Precocious puberty	86.08 ± 8.08	87.42 ± 9.01	0.496
	Hypertension	79.00 ± 6.97	86.62 ± 8.04	**0.002**
	Hirsutism	85.98 ± 8.13	88.44 ± 8.32	0.223
	Urinary incontinence	81.25 ± 8.96	86.31 ± 8.13	0.220
	Hyperpigmentation	83.69 ± 9.31	86.94 ± 7.67	**0.018**
	Short stature	87.50 ± 7.12	86.83 ± 9.22	1.00
	TART	83.33 ± 4.04	86.25 ± 8.20	0.54
	PCOS	86.20 ± 8.18	88.00 ± 0.00	0.826
Psychological domain (100)	Precocious puberty	74.32 ± 8.56	74.60 ± 9.43	0.893
	Hypertension	68.36 ± 9.72	74.93 ± 8.44	**0.014**
	Hirsutism	69.78 ± 10.47	75.04 ± 8.30	**0.013**
	Urinary incontinence	59.50 ± 12.01	74.88 ± 8.30	**<0.001**
	Hyperpigmentation	70.91 ± 10.03	75.63 ± 7.89	**0.001**
	Short stature	67.67 ± 14.88	74.00 ± 7.98	0.589
	TART	77.00 ± 3.46	74.53 ± 8.67	0.624
	PCOS	69.00 ± 0.00	74.60 ± 8.63	0.518
Social domain (100)	Precocious puberty	71.22 ± 11.07	71.47 ± 14.31	0.927
	Hypertension	64.55 ± 9.45	71.63 ± 11.38	**0.044**
	Hirsutism	66.39 ± 16.59	71.73 ± 10.67	0.057
	Urinary incontinence	53.00 ± 6.00	71.62 ± 11.16	**0.001**
	Hyperpigmentation	65.29 ± 14.37	72.97 ± 9.74	**<0.001**
	Short stature	68.5 ± 7.12	60.33 ± 16.75	0.485
	TART	75.0 ± 0.0	71.19 ± 11.45	0.566
	PCOS	71.23 ± 11.4	75.00 ± 0.0	0.742
Environmental domain (100)	Precocious puberty	81.37 ± 5.58	82.74 ± 7.32	0.324
	Hypertension	80.64 ± 4.52	82.72 ± 5.81	0.243
	Hirsutism	79.17 ± 6.41	82.95 ± 5.59	**0.007**
	Urinary incontinence	79.50 ± 3.0	82.67 ± 5.79	0.276
	Hyperpigmentation	80.31 ± 5.89	83.28 ± 5.56	**0.002**
	Short stature	83.33 ± 3.62	82.33 ± 7.47	0.699
	TART	83.33 ± 4.04	82.60 ± 5.79	0.827
	PCOS	82.58 ± 5.76	88.00 ± 0.0	0.349
Total score (400)	Precocious puberty	314.58 ± 25.39	314.64 ± 32.81	0.993
	Hypertension	292.55 ± 20.13	315.92 ± 25.86	**0.004**
	Hirsutism	303.78 ± 33.99	315.70 ± 25.04	0.064
	Urinary incontinence	273.25 ± 26.55	315.47 ± 25.45	**0.001**
	Hyperpigmentation	300.2 ± 32.04	318.82 ± 22.53	**<0.001**
	Short stature	312.67 ± 17.68	297.83 ± 41.99	0.589
	TART	318.67 ± 6.51	314.57 ± 26.27	0.788
	PCOS	314.6 ± 26.15	320.0 ± 0.0	0.837

CAH, congenital adrenal hyperplasia; PCOS, polycystic ovary syndrome; QOL, quality of life; SD, standard deviation; TART, testicular adrenal rest tumor. Bold values are statistically significant.

with higher levels of testosterone showed statistically significant lower scores at the physical domain ($r = -0.303$, $p = 0.05$).

Patients with frequent hospital admissions within the last year had lower QOL scores at the physical and environmental domains, and total scores ($p < 0.001$, 0.047 and <0.001, respectively) (Tables 3 and 4).

Regarding CAH complications, patients with hypertension had lower scores at all domains except the environmental domain and those with hirsutism showed statistically significant lower scores at the psychological and environmental domains ($p = 0.013$, 0.007, respectively). Patients who suffered from urinary incontinence as a complication of genital surgery showed lower scores at the psychological ($p < 0.001$) and social ($p = 0.001$) domains as well as total QOL scores (Table 5).

Discussion

Many studies that investigated QOL in adults with CAH, especially females, focused on exploring the influence of atypical sex hormone exposure during brain development, while only few researches have been carried out to study the QOL in children [15–18]. In all studies, researchers used many different questionnaires as there was no specific questionnaire for CAH. So, it was difficult to compare the results directly due to the use of different instruments to assess HRQOL.

The current study showed an overall decrease in HRQOL in children and adolescents with CAH and that the psychological and social domains showed lower scores than the physical and environmental domains. This came in concordance with the study by Yau on children with CAH using the PedsQL 4.0 questionnaire in which he reported lower overall HRQOL compared to the general population. Greater percentage of children with CAH felt that their physical, emotional, social and school functioning were impaired compared to the general pediatric population [15]. Another study using the CHQ and PedsQL 4.0 questionnaires reported that self-assessment of HRQOL showed significantly lower scores for physical, psychosocial and total scores when compared to healthy children and adolescents due to damage caused by the disease or the need for continued treatment [12]. Several studies reported similar findings of increased rates of psychiatric symptoms among children and adolescents with CAH [15, 19, 20–23]. The study by Wang and Tian on children with disorders of sex development (DSD) including CAH using WHOQOL-BREF showed that scores of the psychological and environmental domains were lower than those of the physical and social domains, but the difference was not significant [20]. In contrast, a study involving children with CAH in a Dutch population showed few negative effects of CAH on physical, social and societal functioning based on a self-designed questionnaire and their QOL was not reduced, and those children experienced several daily health-related problems that did not hamper them in their daily activities and their participation in the society [16].

Comparing males to females in the current study, results showed that females had statistically significant lower scores at the psychological domain, which may be due to the presence of genital ambiguity and the need for genital surgery, while males showed statistically significant lower scores at the physical domain, which might be related to the fact that males are usually diagnosed late compared to females (as genital ambiguity at birth helps their earlier diagnosis and management). Similarly, Crawford's study showed that female children and their parents reported slightly lower psychosocial QOL compared to healthy children and their parents [24]. Engberg and his colleagues found a higher risk of psychiatric disorders among girls and women with CAH compared to controls [21]. According to Zainuddin, females with CAH have many issues to deal with in their lives: chronic medical condition, life-long medications and follow-ups, surgery with its associated consequences, psychosexual issues, body image and psychological consequences, and poor reproductive outcome affecting their QOL [22]. In contrast to our study, Gilban and Yau in separate studies reported no difference in HRQOL when comparing males and females with CAH [12, 15], whereas Idris and his colleagues reported that internalizing behavioral problem was prevalent among boys with CAH reflecting maladaptive adjustment in coping with chronic illness, although psychosocial adjustment of girls with CAH was found to be similar to unaffected female controls and was within the normal population range [25]. Another study involving CAH males showed increased psychiatric morbidity that was not related to their genotype, which improved after implementation of neonatal screening owing to earlier diagnosis [23].

Results of comparison between the clinical types of CAH in relation to different WHOQOL domains revealed that SW CAH patients had shown statistically significant lower scores at the physical domain than SV CAH patients. This was similar to the study by Gilban that reported no significant difference between SW and SV, except in the physical dimension [12]. Similarly, Mueller and colleagues found no difference in psychiatric morbidity between those with the SW and SV phenotype [18], whereas Yau

found no difference in HRQOL regarding the clinical type of CAH [15].

Females who had undergone clitoroplasty showed statistically significant higher scores at the psychological domain compared to those who were not operated. This was similar to the results of Fagerholm who reported that females after feminizing genitoplasty had good QOL and mental health as they had less distressing symptoms [26]. Also, other studies showed that patients after feminizing genitoplasty did not have significant psychological maladjustment [27, 28]. However, worse results have been reported due to either too late genital treatment, poor surgical outcome or distressful memories. These may have been associated with psychiatric symptoms and poor QOL after genitoplasty [29, 30]. In our cohort, 56.2% of the males were reassigned as females at an early age owing to the early diagnosis and social factors in our community that necessitates sex differentiation as early as possible.

Correlation between the timing of surgery and QOL showed that patients who had undergone clitoroplasty at an older age showed statistically significant lower QOL scores at the psychological domain. This was similar to the study by Savanelli who reported that early surgery and early creation of an external genitalia appearance that matches the genetic sex may contribute to reducing the anxiety of parents and children, helping them to cope better psychologically on a daily basis without embarrassment [31]. Similarly, Berenham reported that psychological adjustment was not compromised in females with virilized genitalia who were treated early in life and that psychological adjustment was not significantly associated with the degree of genital virilization, the appearance of external genitalia or the age at genital surgery [28], as early surgery in girls would lead to better psychosocial and psychosexual adjustment [32]. Idris, on the contrary, showed no correlation between behavioral outcome or psychological adjustment and age of genitoplasty in females with CAH [25]. Cull reported that genital surgery in childhood often led to feelings of loss of body ownership and resentment [33]. Nordenskjold also reported that the overall QOL in females with CAH was affected by the operative procedure in itself [34]. Despite the controversies surrounding the timing of surgery, the evidence available supported early feminizing genitoplasty [35–39]. Patients who suffered urinary incontinence as a complication of genital surgery showed lower scores at the psychological and social domains as well as total scores. Also, Nordenskjold reported that the overall QOL in females with CAH was affected by postoperative complications such as vaginal stenosis or incontinence [34].

In our cohort, older children and adolescents showed lower QOL scores at the psychological and social domains as well as total scores. This came in contrast to Yau who reported no statistically significant differences in the overall HRQOL or specific domains with regard to age [15].

We found no relation between QOL and age at diagnosis of CAH. This was similar to the results of Idris who reported no correlation between behavioral outcome or psychological adjustment and the mean age at diagnosis [25]. On the contrary, Falhammar reported that male CAH patients with late diagnosis were more depressive ($p = 0.011$) and had lower self-control ($p = 0.019$) and that early diagnosis of DSD (including CAH patients) was associated with less comorbidities [40, 41].

In our study, patients with higher Tanner staging showed statistically significant lower scores at the social domain, which might be related to age and disease duration. Pubertal patients being adolescents are more concerned about their well-being and more scared about life-long complications of their chronic illness, and more annoyed about long-term medications. Meanwhile, patients with a higher Prader score (more virilized) showed statistically significant lower scores at the physical domain and total scores as it might be related to high adrenocorticotropic hormone (ACTH) exposure. This came in contrast to Idris who showed no correlation between behavioral outcome or psychological adjustment and Prader rating [25].

Patients with frequent hospital admissions within the last year in our study had lower QOL scores at the physical and environmental and domains, and total scores. Also, Nordenskjold reported that his patients had identified experiences that have negatively impacted their QOL, including hospitalizations for adrenal crisis [34]. Similarly, other studies showed that adrenal crisis during childhood had a significant impact on HRQOL [42, 9].

Patients compliant with treatment showed statistically significant higher scores at the social and environmental domains, and total scores compared to those who were non-compliant. Patients following up regularly at our clinic showed statistically significant higher scores at the environmental domain as easy access to medical services and regular follow-up led to better HRQOL. Also, good compliance with treatment with regular follow-up ensures adequately controlled CAH with less complications, so higher HRQOL. The study by Mnif et al. showed that many of the low health outcomes in CAH appeared to be related to poor adherence to medication schedules and poor hormonal control [43].

Comparing between patients who experienced complications of CAH and those who did not develop complications in relation to WHOQOL domains, hirsutism (in females) and hypertension affected QOL in our cohort

compared to other complications. Similarly, Wang and Tian reported that CAH patients who developed chronic illnesses such as hypertension scored less in physical and social relationship and environmental domains [20]. Kamoun reported that patients with CAH had many factors that could influence their QOL, such as genital surgery procedure, short stature and hirsutism [44].

In our study, glucocorticoid dose did not affect QOL. Similarly, Yau found no correlation between QOL and dose of hydrocortisone [15]. However, we found that patients receiving large doses of mineralocorticoids showed lower QOL scores at the psychological domain and total scores of WHOQOL. This might be attributed to the fact that patients with large doses of mineralocorticoids had more severe SW CAH, and thus lower QOL scores.

Levels of 17-OHP in our study did not affect QOL except in the physical domain. Similarly, Han reported that impaired QOL in patients with CAH was related to patients' poor disease control [45]. However, Idris showed no correlation between behavioral outcome or psychological adjustment and serum 17-OHP [25]. Patients with high serum levels of Δ4 androstenedione within the last year showed lower scores at the psychological and social domains, and total score of WHOQOL indicating the importance of adequate control. So, serum levels of Δ4 androstendione might be more important in monitoring CAH. However, we found no statistically significant correlation between QOL and serum testosterone levels within the last year except in the physical domain. This was similar to Idris who reported no correlation between behavioral outcome or psychological adjustment and serum testosterone levels at the time of his study [25]. On the contrary, Falhammar reported that QOL score positively correlated with adrenal androgens and steroid precursors in male CAH cases [40].

Conclusions

HRQOL was relatively more affected in CAH patients with older age, poor hormonal control, high frequency of hospital admissions and those who developed complications.

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