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Research Article

Quality of Life in Children Diagnosed with Non-Classic Congenital Adrenal Hyperplasia

Maria João Silva Ferreira*

Centro Hospitalar Universitário São João, E.P.E. Rua Nove de Abril, 431 hab 55 4250-348, Porto, Portugal

ABSTRACT

Introduction: Non-classical congenital adrenal hyperplasia (NC-CAH) is a chronic disease characterized by excessive androgen production that may negatively affect quality of life (QoL) of affected patients. Pediatric Quality of Life Inventory 4.0 (PedsQL) is a validated tool to assess health-related QoL (HRQoL).

Methods: Cross-sectional study including 19 patients with NC-CAH followed in the pediatric endocrinology department. NC-CAH patients who agreed to participate were included. Anthropometric data was collected. PedsQL™ was applied to the patients and their parents. Patients were divided into four groups according to age: 2-4, 5-7, 8-12 and 13-18 years-old. Control group consisted of healthy individuals from the instrument's validation studies for the Portuguese population and the standard control population used in the PedsQL validation study.

Results: The only difference found concern the parents' score results of children aged 8-12, whose results showed physical health and emotional dimension' scores significantly higher (86.16 ± 9.86 vs 68.90 ± 23.02 p=0.004, 69.17 ± 14.14 vs 65.82 ± 19.24 p=0.004), while psychosocial health's score and total scale score were significantly lower than the control group (59.99 ± 9.90 vs 69.34 ± 14.07 p=0.047, 73.11 ± 4.65 vs 78.86 ± 16.61 p=0.017).

Conclusion: HRQoL scores are not negatively affected by NC-CAH on most group ages, with the exception of the parents' reports on HRQoL of children aged 8-12. Further studies with a greater number of patients are needed to determine the impact of this chronic disease on the HRQoL of children.

Keywords: Quality of life; Health related quality of life; Congenital adrenal disease; Non classical congenital adrenal disease

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an autossomic recessive disorder of cortisol synthe-sis pathway that is most commonly caused by the mutation of the CYP21A1 gene [1,2]. This results in an enzyme deficiency in the adrenal cortex leading to, in over 90% of the cases, 21-hidroxilase deficiency (21-OHD) [3-6]. The hallmark of this disease is excessive androgen production, resulting from the impaired or no conversion of 17-hydroxyprogesterone (17OHP) to 11-deoxycortisol and of progesterone to deoxycorticosterone [7]. The blockade of steroid conversion results in increased androgen precursors production under CRH-ACTH stimulation, leading to biochemical hyperandrogenism, marked by elevated 17-OHP levels, with variable gravity according to different phenotypes [8,9]. As so, the disease presents a broad spectrum, ranging from severe forms (classical CAH) to mild forms (non-classical CAH). The non-classical form (NC-CAH) is characterised by a less severe deficiency and manifests as increasing virilisation before puberty without genital ambiguity [10]. NC-CAH is more prevalent than the classic form, estimated to affect 0.1%-0.2% of the population [11]. It is also more frequently observed in females, as males with NC-CAH have less recognized signs of androgen excess [12]. Androgen excess in NC-CAH patients can lead to premature pubarche in children and to ovarian hyperandrogenism in adolescence. Affected patients may present signs of androgen excess, such as acne, hirsutism, apocrine body odor, irregular menses and advanced bone age, which may lead to short adult height [13].

In contrast to classical CAH patients, adrenal replacement is not required in NC-CAH patients [14]. Pharmacological treatment is focused on the management of signs of hyper-androgenism. Children with NC-CAH should be treated for inappropriately early onset of body hair and odour when bone maturation is sufficiently accelerated to adversely affect future height. Clinicians can

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Correspondence to: Maria João Silva Ferreira, Endocrinology Resident at Centro Hospitalar Universitário São João, E.P.E. Rua Nove de Abril, 431 hab 55 4250-348, Porto, Portugal, Tel:+351910045552; E-mail: mj.ferreira0@gmail.com

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withhold treatment with careful monitoring if advanced bone age is not present. In children, treatment consists of glucocorticoids in doses aimed at suppressing hyperandrogenism, which are usually higher than the physiologic replacement and do not mimic the physiological circadian rhythm of cortisol. In adolescents with irregular menses and acne, symptoms are usually reversed within 3 months of treatment with GC, whereas hirsutism remission is more difficult with GC monotherapy. In such cases, an oral contraceptive with or without anti-androgens is likely the best approach. Once near-adult height has been reached, tapering and discontinuing GC treatment should be consid-ered. Awareness of a medical condition, symptoms of hyperandrogenism and consequent virilisa-tion, the burden of daily medication administration, the fear of an adrenal crisis and fluctu-ating adrenal androgens levels may negatively impact quality of life (QoL) of CAH pa-tients [15]. Health-Related QoL (HRQoL) has been increasingly used as a supplement to clinical treat-ments, ensuring that the patients' perspective on the disease, the need for care and their preferences for treatment modalities are considered. HRQoL in patients with CAH (including NC-CAH) has been widely studied, however, to our knowledge, investigation on HRQoL of NC-CAH patients exclusively is scarce [16].

We aimed at evaluating the health-related quality of life of pediatric patients with NC-CAH. We report scores from the validated Pediatric Quality of Life Inventory 4.0 (PedsQL).

METHODS

Cross-sectional study including 19 patients with NC-CAH followed in the pediatric endocri-nology department. Patients diagnosed with NC-CAH who agreed to participate were includ-ed. NC-CAH diagnosis was made by elevated 17OHP levels in cosyntropin stimulation test, which is accepted as the gold standard for NC-CAH diagnosis. All patients were referred to genetic consultation and all had CYP21A2 gene mutations. Exclusion criteria were refusal and/or incapacity to answer the questionnaire and the presence of other comorbidities which may interfere results. No patient or parent refused to participate. Three patients were excluded as they missed the medical appointment and the medical staff was unable to contact them. One child was excluded because of the presence of multiple comorbidities not related to the disease, which could possibly affect the assessment of HRQoL.

Clinical follow-up of patients in our unit included measurements of weight (by a standard calibrated scale) and height (by a stadiometer) of patients. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared and the growth chart percentiles of the Centers for Disease Control and Prevention were registered.

Patients were divided into four different groups according to their ages: 'toddlers'-2-4 years-old-(2 patients), 'young children'-5-7 years-old-(1 patient), 'children'-8-12 years-old-(7 patients) and 'adolescents'-13-18 years-old-(9 patients). The Portuguese version of Pediatric Quality of Life Inventory 4.0 (PedsQL™) was used to evaluate HRQoL. PedsQL™ has been widely used in previous studies that assessed HRQoL in children and adolescents. It has been translated and validated for use in Portuguese population [17,18]. It presents different versions for age group, respecting the cognitive development of children. For children, the following versions are available: 5–7 years of age (interview); 8–12 years, and 13–18 years. For parents, 2–4, 5–7, 8–12 and 13–18 age groups versions are available. Its questions cover physical functioning (eight items), emotional dimension (five items), social dimension (five items) and scholar dimension (five items). The items of the different age versions are essen-tially similar, differing only in appropriate language for each stage of cognitive development. Items are scored on a 5-point Likert scale for children and adolescents and for the parents' versions. In this scale, zero (0) means never, and four (4) means almost always. In the 5–7 children versions, the faces scale uses the anchors 0 (never), 2 (often) and 4 (very often). Items are inversely scored and linearly transformed from zero (0) to one hundred (100) (0=100, 1=75, 2=50, 3=25 and 4=0). Scores were obtained for each of the measured scales and grouped into two major dimensions: physical health (physical functioning items), psychosocial health (emotional, social, and school functioning items) and in a total score, resulting from the sum of all items, divided by the number of the items with a valid answer. Higher scores point to a better HRQoL. If more than 50% of items are missing for a scale, the score is not given.

The group used as control consisted of healthy individuals from the instruments' previously published validation studies for the Portuguese population of children between age 5-7 and 8-12. For patients aged 2-4 and 13-18, the results of the study survey were compared to a standard control population used in the PedsQoL validation study [19].

All the categorical variables were described using frequencies and percentages and the con-tinuous variables were presented using means and standard deviations or median and inter-quartile range, as appropriate. One sample T test was performed for associations between PedsQL scores by the five different groups and those reported by groups used as controls. Children's and parent's reports were compared using two sample T test. Regarding 5-7 age groups, no statistical analysis was performed, as it was constituted by only one patient. A p value of<0.05 was considered significant. Statistical analysis was performed with the Statis-tical Package for the Social Sciences (SPSS) software, version 20.0 (IBM, Armonk, New York, USA).

This study was approved by the Hospital Ethical Comittee. All eligible participants agreed to participate in the study and provided parental informed consent.

RESULTS AND DISCUSSION

Characterization of the population

Nineteen patients were included, 13 (68.4%) girls and 6 (31.6%) boys. The median age was 11.9±4.9 years. Regarding diagnosis, 7 (36.8%) patients were referred to a pediatric endocrinologist for signs of premature pubarche, 4 (21.1%) for family history, 3 (15.8%) for axillary apocrine odor, 3 (15.8%) for hirsutism, 1 (5.3%) for oligoamenorrhea and 1 (5.3%) was diagnosed while studying an adrenal mass. The mean BMI was 20.2kg/m2, corresponding to a mean Percentile (Pc) of 61.9. Five patients (26.3%) were overweight and 2 (10.5%) obese. Of those, 3 female patients (15.8%) and 2 (10.5%) male patients were overweight; 2 (10.5%) male patients were obese. Boys with excess weight corresponded to 66.7% of the male patients. Fifteen (84.2%) patients were under treatment with hydrocortisone. The characteristics of patients are summarized in Table 1.

Table 1: Patients characteristics.

	Female patients	Male patients	Total
Patients, n(%)	13 (68.4)	6 (31.6)	19 (100)
Median age	13.4	8.7	11.9 +-4.9
Signs/symptoms			
Premature adrenarche, n(%)	6 (46.2)	1 (16.7)	7 (36.8)
Axillary apocrine odor, n(%)	0 (0.0)	3 (50.0)	3 (15.8)
Hirsutism, n(%)	3 (23.1)	0 (0.0)	3 (15.8)
Oligoamenorhea, n(%)	1 (7.7)	-	1 (5.3)
Family history, n(%)	3 (23.1)	1 (16.7)	4 (21.1)
Other, n(%)	0 (0.0)	1(16.7)	1 (5.3)
BMI (kg/m2 mean, mean Pc)	20.0 (55.5)	20.6 (74.7)	20.2 (61.9)
Hydrocortisone treatment (n, %)	12 (91.7)	4 (66.7)	16 (84.2)
Dose of hydrocortisone per body surface area (mean, mg/kg/day)	7.8	7.2	7.5

HRQoL assessments: HRQoL assessments are summarized in Tables 2-5.

Toddlers (2-4 age group)

Parent's HRQoL scores: Parent's reports on total score 2-4 age group was similar to the one reported, (75.20 ± 5.40 vs 87.42 ± 12.49). Statistical analysis was not computed due to small sample size.

Young children (5-7 age groups)

Self-assessment HRQoL scores: This group consisted of only one patient. Even though it was not possible to perform statisti-cal analysis comparing to the control population, our patient presented a higher score in every item of the questionnaire. Children's self-assessment scores were also similar to the ones reported, (85.40 vs 81.86±12.64).

Parent's HRQoL scores: HRQoL score assessed by the parents had a higher score than the mean of the Portuguese control group on every item, besides the parent's report on emotional functioning (50.00 vs 68.83 ± 16.97) and on school functioning (65.00 vs 65.69 ± 21.32).

Parent's report score on total scale score on the 5-7 age group was similar to the one re-ported, (76.50 vs 78.02 ± 16.61). Statistical analysis was not performed due to small sample size.

Table 2: PedsQL scores.

PedsQL scores		2-4 age group		5-7 age group		8-12 age group		13-18 age group	
Children's reports	Total scale score	-	-	85.40	-	80.38	9.11	84.24	9.18
	Physical health	-	-	87.50	-	87.41	13.31	84.49	12.08
	Psychosocial health	-	-	83.30	-	73.34	6.95	83.33	9.45
	Emotional functioning	-	-	80.00	-	65.83	12.81	73.89	21.03
	Social functioning	-	-	100.00	-	85.00	14.14	91.11	8.58
	School functioning	-	-	70.00	-	69.17	11.58	85.00	8.66
Parent's reports	Total scale score	75.20	5.40	76.50	-	73.11	4.65	83.91	11.13
	Physical health	81.27	9.37	81.30	-	86.16	9.86	87.50	14.73
	Psychosocial health	69.20	1.40	71.80	-	59.99	9.90	80.19	10.80
	Emotional functioning	80.00	14.14	50.00	-	69.17	14.14	64.44	23.38
	Social functioning	65.00	14.14	100.00	-	69.17	21.31	89.44	11.02
	School functioning	62.50	5.94	65.00	-	61.67	8.76	86.67	9.01

Note: s.d.: standard deviation

Table 3: Comparison between scores of 5-7 and 8-12 children with the Portuguese control group [16].

PedsQL scores		**5-7 age study group**		**5-7 age control group**		**p- value**	**8-12 age study group**		**8-12 age control group**		**p- value**
		mean	**s.d.**	**mean**	**s.d.**		**mean**	**s.d.**	**mean**	**s.d.**	
Children's reports	Total scale score	85.40	~	75.45	12.04	~	80.38	9.11	75.74	14.270	0.226
	Physical health	87.50	~	77.39	18.42	~	87.41	13.31	78.04	19.55	0.110
	Psychosocial health	83.30	~	74.41	10.99	~	73.34	6.95	74.52	13.81	0.675
	Emotional functioning	80.00	~	74.71	15.88	~	65.83	12.81	70.05	18.25	0.452
	Social functioning	100.00	~	76.32	14.85	~	85.00	14.14	80.72	17.84	0.489
	School functioning	70.00	~	72.21	17.69	~	69.17	11.58	72.79	15.16	0.477
Parent's reports	Total scale score	76.50	~	68.78	17.28	~	73.11	4.65	69.19	15.48	0.068
	Physical health	81.30	~	68.40	21.40	~	86.16	9.86	68.90	23.02	0.004*
	Psychosocial health	71.80	~	68.98	16.88	~	59.99	9.90	69.34	14.07	0.047*
	Emotional functioning	50.00	~	65.83	16.97	~	69.17	14.14	65.82	19.24	0.004*
	Social functioning	100.00	~	75.42	21.92	~	69.17	21.31	76.23	20.01	0.456
	School functioning	65.00	~	65.69	21.32	~	61.67	8.76	65.98	16.04	0.289

Table 4: Comparison between study sample and original study sample [17].

PedsQL scores		Study sample		Varni, et al		p value
		mean	s.d.	mean	s.d.	
Children's reports	Total scale score 2-4 age group	~	~	~	~	
	Total scale score 5-7 age group	85.40	~	81.86	12.64	~
	Total scale score 8-12 age group	80.38	9.11	83.31	13.45	0.427
	Total scale score 13-18 age group	84.24	9.18	83.65	13.30	0.851
Parent's reports	Total scale score 2-4 age group	75.20	5.40	87.42	12.49	~
	Total scale score 5-7 age group	76.50	~	78.02	16.44	~
	Total scale score 8-12 age group	73.11	4.65	78.86	16.61	0.017*
	Total scale score 13-18 age group	86.67	9.01	79.45	16.40	0.264

Note: s.d.: standard deviation ; * statistically significant

Table 5: Comparison between children's reports and parent's reports.

PedsQL scores	**1(16.7)**	**1(16.7)**	**1(16.7)**	**1(16.7)**	**p value**
	mean	**s.d.**	**mean**	**s.d.**	
8-12 age group	80.38	9.11	73.11	6.95	0.084
13-18 age group	83.74	9.68	84.85	11.5	0.837
Total	82.72	8.79	78.62	10.06	0.193

Children (8-12 age groups)

Self-assessment HRQoL scores: Self-evaluated children aged 8-12 years' HRQoL scores were similar to that obtained by the Portuguese control group. Total scale score, physical health, and social functioning' scores were higher than the ones reported by the Portuguese control group (80.38 ± 9.11 vs 75.74 ± 14.27 p=0.226; 87.41 ± 13.31 vs 78.04 ± 19.55 p=0.110; 85.00 ± 14.14 vs 80.72 ± 17.84 p=0.489, respectively). On the other hand, psychosocial health, emotional dimension and school dimension' scores were lower than the ones reported by the same control group (73.34 ± 6.95 vs 74.52 ± 13.81 p=0.675; 65.83 ± 12.82 vs 70.05 ± 18.25 p=0.452; 69.17 ± 11.58 vs 72.79 ± 15.16 p=0.477).

Children's self-assessment score on total scale score on the 8-12 age group was also similar to the one reported by Varni, et al (80.38 ± 9.11 vs 83.31 ± 13.45 p=0.427).

Parent's HRQoL scores: Parent's reports of total HRQoL scores of children aged 8-12 was similar to those reported by the control group (73.11 ± 4.65 vs 69.19±15.48 p=0.068), as well as the social and school functioning score (69.17 ± 21.31 vs 76.23 ± 20.01 p=0.456, 61.67 ± 8.76 vs 65.98 ± 16.04 p=0.289). Physical health and emotional dimension' scores were significantly higher than the control group (86.16 ± 9.86 vs 68.90 ± 23.02 p=0.004, 69.17 ± 14.14 vs 65.82 ± 19.24 p=0.004). Psychosocial health's score, on the other hand, was significantly lower than the one present-ed by the control group (59.99 ± 9.90 vs 69.34 ± 14.07 p=0.047).

Parent's report score on total scale score on the 8-12 age group was significantly lower compared to the control sample by (73.11 ± 4.65 vs 78.86 ± 16.61 p=0.017).

Adolescents (13-18 age group)

Self-assessment HRQoL scores: Older children's self-assessment score on total scale by the 13-18 age group was similar to the control group (84.24 ± 9.18 vs 83.65 ± 13.30 p=0.851).

Parent's HRQoL scores: Parent's report on total scale score (86.67 ± 9.01 vs 79.45 ± 16.40 p=0.264) was similar to the control group.

Parent's and children's HRQoL total scores: Parent's and children's reports on total scale score did not differ (78.62 ± 10.06 vs 82.72 ± 8.79 p=0.193), neither in 'young children' and 'adolescents' groups (80.38 ± 9.11 vs 73.11 ± 6.95 p=0.084 and 83.74 ± 9.68 vs 85.85 ± 11.5 p=0.837)

DISCUSSION

Our study evaluated the quality of life of children with NC-CAH. 'Toddlers', 'young children' and 'adolescents' self-assesment and parent's reports on HRQoL showed no significantly overall difference between patients with NC-CAH and control groups. Parent's report score results of children aged 5-7 were lower on emotional and school functioning, however with-out statistical significance. This is in line with previous reports, who exam-ined NC-CAH patients and compared them to their healthy siblings and showed no differ-ence between the total scores and the scale and sub-scale scores for HRQoL [11]. A Dutch study involving children with CAH, including NC-CAH, and their parents also showed no re-duction in HRQoL of these patients [20].

Physical health scores of our study show no differences between NC-CAH patients and con-trol groups, with the exception of parents children aged 8-12' scores, which were signifi-cantly higher. Psychosocial health' scores, including emotional, social and school dimension, are similar between our study group and control groups in 'toddlers', 'young children' and 'adolescents'. This is in line with other studies that show that appropriately treated children and adoles-cents with NC-CAH have social and school dimension HRQoL scores similar to healthy popu-lations. This is encouraging, as early exposure to hyperandrogenism may affect cognitive functions, including social behavior patterns, which is a major parental concern [21,22].

On the other hand, 'children' (aged 8-12) self-assessment HRQoL scores showed lower re-sults on psychosocial health, emotional dimension and school dimension' scales than the control group, however without statistical significance. Parent's HRQoL scores were signifi-cantly lower on the psychosocial health score than the Portuguese control group, social and school dimensions being the items responsible for this result. Total scale score was also significantly lower in comparison to the control population. This has also been observed who demonstrated a lower total scale score by the Portuguese population comparing to the control population. The authors hypothesized that this decline in quality of life may be associated with the phase of pre-adolescence, often characterized by changes in school and in personal relationships, new development tasks that lead to more responsibility for the child. Thus, this period may be associated with some socio-emotional instability that can explain this decline, has also showed that the emotional score of NC-CAH patients and parent's scores were significantly lower compared to the healthy USA pediatric population. Other studies have shown that parents of children with chronic disease over-report lower HRQoL compared to their child, including patients with CAH [23].

Excess weight was present in 42.8% of our study. Interestingly, 50% of our patients with ex-cess weight/obesity were between 8-12 years old, which was the age range that presented more differences to the control population. Obesity and increased metabolic risk has been reported in young patients with CAH, and has been found to have a negative effect in many domains of HRQoL, namely on the physical, social and school functioning domains [24,25]. Significantly impaired subjective health status in CAH adult patients (including NC-CAH pa-tients), especially in the domains of general health, vitality and role limitations due to emotional problems, as well as increased anxiety scores have also been demonstrated. In our study, however, significantly higher results on physical and emotional functioning scores reported by children aged 8-12' parents were observed. The fact that older children perceive themselves as more physically capable was also noted [17]. Nonetheless, this is against what is usually observed in obese and overweight children [26].

Quality of life in adult patients with CAH (sometimes including NC-CAH patients) has been widely studied, some studies showing an overall impaired self-reported quality of life [27,28] whilst others showed no difference [29]. Studies involving adolescents and children are more limited, as well as those exclusively studying NC-CAH patients.

Limitations to our study include the small sample size, which probably reflects the underdi-agnosis and undertreatment of NC-CAH patients. Another limitation may be the lack of comparison between NC-CAH patients and similar aged healthy children which share the same environment, as well as lack of Portuguese control group for toddlers and adolescents. Our strengths include the uniformity of medical diagnosis (cosyntropin stimulation testing and genetic confirmation of CYP21A2 gene mutations) as well as of the adherence to treat-ment and surveillance in a single medical center.

CONCLUSION

Our study examines the HRQoL in a pediatric cohort comprised solely of NC-CAH patients. Our findings suggest that HRQoL scores are not negatively affected by NC-CAH on most group ages, with the exception of the parent's reports on HRQoL of children aged 8-12. Par-ents lower report on HRQoL has been previously described in children with chronic diseases. Our results are reassuring, as adequate treatment and follow-up of these patients seems to allow them to have a QoL compared to the healthy population. Nonetheless, attention should be directed to this particular group and understand the reason for these lower scores. Further studies with a greater number of patients are needed in order to determine the impact of this chronic disease on the quality of life of children.

AUTHOR CONTRIBUTIONS

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission

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