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Health-related quality of life and fatigue perception in children with congenital adrenal hyperplasia: A Developing nation perspective

Jakość życia związana ze zdrowiem i postrzeganie zmęczenia u dzieci z wrodzonym przerostem nadnerczy: perspektywa kraju rozwijającego się

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Abstract

Introduction: Disease chronicity, lifelong medications, Adrenal crisis, and genital surgeries affect the physical, mental, school and social aspects of a child's life and are a cause of great concern to parents regarding the future of their child with Congenital Adrenal Hyperplasia (CAH). The aim of the study was to assess quality of life (QoL) in children and parents of CAH and comparison with healthy children.

Material and methods: This was a questionnaire-based cross-sectional study in 28 children with classical CAH attending the Pediatric Endocrine clinic at a tertiary-care center in northern India.

Results: CAH children had poorer QoL in School domain (73.6 vs. 90.0; $p = 0.034$) and significantly lower scores than their healthy peers in General (83.1 vs. 91.7, $p = 0.025$), Sleep (74.4 vs. 84.2, $p = 0.017$) domains and total score (80.0 vs. 87.8, $p = 0.008$) of the Fatigue scale. Parents reported Social (72.4 vs. 84.5; $p = 0.009$), School (63.8 vs. 90.0; p 0.01) and Total (74.3 vs. 84.2; $p = 0.024$) QoL were scores significantly lower than parents of healthy children. Parents perceived scores of Fatigue scale were significantly worse in all domains when compared to parents of healthy children. Failure to thrive was found to be a significant risk factor for impaired school ($r = –0.533$; $p = 0.013$) and overall ($r = –0.563$; $p = 0.008$) QoL as perceived by the child.

Conclusions: Children and parents have different perception of QoL for their child. Routine periodic QoL assessment will help in better understanding of child and parent's hidden concerns which remain unaddressed in busy clinical practice.

Key words:
congenital adrenal hyperplasia, fatigue, quality of life.

Introduction

Congenital adrenal hyperplasia (CAH) is an inherited disorder of adrenal steroid hormone synthesis leading to decreased cortisol production, mineralocorticoids, and increased secretion of sex steroids like DHEAS. The classical salt wasting CAH presents in neonatal age with genital ambiguity in females ranging from clitoromegaly to completely male like genitilia and hyperpigmentation, adrenal crisis manifesting as hypovolemia, acidosis, electrolyte imbalance and shock in both sexes. Male babies are frequently missed and die due to lack of diagnosis and treatment especially in countries with no newborn screening program. The simple virilizing form of classical CAH present with genital ambiguity in female and precocious puberty in both sexes in childhood. The nonclassical forms present in adolescents and adults with acne, clitoromegaly, infertility. CAH treatment requires lifelong glucocorticoid and mineralocorticoid replacement, surgery for ambiguous external genitalia in affected females, and hospital admissions for adrenal crisis. The complications related to disease and treatment such as precocious puberty, compromised growth, overtreatment and undertreatment with steroids, gender dysphorias and concerns for future fertility disturbs the peace of mind for child and caregivers. All these factors affect a child's physical, mental, school, and social aspects and are a great concern to parents regarding their child's future [1].

Multiple studies reported more inferior QoL in adults with CAH, but data in children are scarce. The concerns and worries are different in both populations. An adult might be more concerned with the appearance of genitalia and the prospect of reproduction. At the same time, a child may be more concerned

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with hospital admission, traveling, and the loss of school days. The absence of a neonatal screening program, only a few specialized centers, and affordability of care compromises India's quality of care of CAH children. Differences in culture, quality, and delivery of care to children with CAH compared to West reiterate the need for specific study for QoL in the former [2–4].

Material and methods

This was a questionnaire-based case-control study in 28 children with classical CAH attending the Pediatric Endocrine clinic at a tertiary-care center in northern India. Age and sex-matched children visiting the immunization clinic of the institute were included as controls. Details were collected regarding the disease's course, including the age of diagnosis, treatment received, significant events (hospitalizations, surgeries), change in the sex of rearing, adverse effects of drugs since these might affect the Health-related QoL.

PedsQL 4.0 Generic scale and Pediatric Fatigue scale were used to measure the Generic core QoL and degree of fatigue in cases and controls. The questionnaire was filled by parents/caregivers of all enrolled children and by children themselves who were above five years of age and could read and understand Hindi or English.

The PedsQL™ Multidimensional Generic Core Scale has 23-items that comprise four sub-scales: 1) physical health (8 items), 2) emotional functioning (5 items), 3) social functioning (5 items), and 4) school functioning (5 items). The scale is comprised of parallel child self-report and parent proxy-report formats. The parent proxy report forms are designed to assess the parents' perceptions of their child's core QoL. Items were reverse-scored and linearly transformed to a 0–100 scale, with higher scores indicating better QoL [5].

The PedsQL™ Multidimensional Fatigue Scale is an 18-item self-report scale that includes three subscales: General (6 items), sleep/rest fatigue (6 items), and cognitive fatigue (6 items). The scale is comprised of parallel child self-report and parent proxy-report formats. Like the PedsQL™ Multidimensional Generic Core Scale, items on the Fatigue Scale were reverse scored and linearly transformed to a 0–100 scale, with higher scores indicating less fatigue [6].

The data was analyzed using SPSS version 23. The mean or median was calculated for normally or not normally distributed data. Independent sample T-test or Mann-Whitney test was used for comparing mean or median in cases and control depending upon the data distribution. Pearson or Spearman coefficients were calculated to find the correlation between various disease factors and QoL scores.

Results

The mean ages of cases (7.5 ±3.2 years) and control (7.5 ±3.5 years) were similar, and females were more than males. Most children had an early presentation with the adrenal crisis or genital ambiguity. All patients were managed with hydrocortisone with and without fludrocortisone, and few required GnRH analogs for precocious puberty. The patients had a mean follow-up of 5.1 ±2.5 years (Table I).

The mean PedsQL 4.0 QoL score of healthy controls ([83.5 ±9.9] for child rated and parents [84.2 ±9.2]) in our study were comparable to the normative data reported in school-going children (87.5 ±11.1) and their parents (90.1 ±9.5) from Kerala, India [5].

CAH children had poorer core QoL in the School domain while Health, Emotional and Social scores were not significantly different from normal peers, but the perception of parents was different as they felt that their child's Social, School, and total core QoL was impaired considerably, while Physical and Emotional QoL were at par with their normal controls (Table II).

CAH children reported significantly lower scores than healthy peers in General, Sleep domains, and the Fatigue scale's total score. At the same time, it was not considerably different in the Cognitive fatigue domain. Parent's perceived worse scores in all Fatigue scale areas than parents of healthy children, namely General, Sleep, Mental and overall domains (Table III).

Table I. Baseline Characteristics of Cases and Control Group

Variable	Cases (n = 28)	Control (n = 35)
Age (years)	7.5 ±3.2	7.5 ±3.6
Sex	M 8 (28.6%), F 20 (71.4%)	M 17 (48.6%), F 18 (51.4%)
Weight Z-score	–0.57 ±1.40	–0.67 ±0.52
Height Z-score	–0.48 ±1.70	–0.05 ±0.58
Body mass index Z-Score	0.51 ±0.94	0.40 ±0.59
Bone age Z-score	0.3	
Median age of diagnosis	M (22 weeks), F (7 weeks)	
CAH type	SW20SV8	
Genital ambiguity at birth	15 (F 15)	
Hydrocortisone dose (mg/m^2)	11 ±3.6	
Precocious puberty (n)	5 (M 2, F 3)	
Sibling loss (n)	3	
Family history (n)	5	
Genital surgery (n)	9	

CAH – congenital adrenal hyperplasia; M – males; F – females; SW – Salt wasting type; SV simple virilizing type

Table II. Comparison of Pediatric Generic QoL scale and Pediatric Fatigue scores in CAH and control Group

Score Domain	Mean±SD / Median*(IQR) Children With CAH (n = 21)	Mean±SD / Median*(IQR) Healthy Control (n = 23)	P value	Mean±SD /Median*(IQR) Parents of Children With CAH (n = 28)	Mean±SD /Median*(IQR) Parents of Healthy Control (n = 35)	P value
Generic QoL score (Total and Subscales)						
Total	79.9 ±11.5	83.5 ±9.9	0.26#	74.3 ±12.8	84.2 ±9.2	0.02#
Physical	82.1 ±12.8	85.6 ±10.5	0.31#	84.4* (15.6)	90.6 (18.8*)	0.88$
Emotional	81.2 ±10.4	81.80 ±13.2	0.86#	80.0* (18)	75.0* (15)	0.63$
Social	90.0* (32.5)	90.0* (40)	0.65$	72.4 ±22.5	84.5 ±20	< 0.01#
School	73.6 ±21.2	90 ±18	0.03#	65* (38)	90* (20)	< 0.01$
Fatigue Scores (Total and Subscales)						
Total	80.0 ±11	87.8 ±6.9	< 0.01#	66.6* (31.9)	87.5* (11.8)	0.04$
General	79.2* (16.7)	91.7* (16.7)	0.03$	75* (35.4)	87.5* (18.7)	< 0.01$
Sleep/Rest	74.4 ±15	84.2 ±10.6	0.02#	70.8* (39.6)	95.8* (16.7)	< 0.01$
Cognitive	91.7* (25)	91.7* (8.3)	0.41$	69.8 ±18	87.2 ±8.1	< 0.01#

*Median (IQR), # t-test, $ Man-Whitney Test

Table III. Comparison of Child self-reported and parent report quality of life scores in CAH children

Score Domain	Mean ±SD /Median*(IQR) Children With CAH (n = 21)	Mean ±SD /Median*(IQR) Parent of children with CAH (n = 21)	P value
Generic QoL score (Total and Subscales)			
Total	79.9 ±11.5	74.3 ±12.8	0.14#
Physical	82.1 ±12.8	81.5 ±13	0.88#
Emotional	80*(17.5)	80*(17.5)	1.00$
Social	81.43 ±18.78	72.4 ±22.5	0.15#
School	73.6 ±21.2	63.8 ±21.6	0.15#
Fatigue Scores (Total and Subscales)			
Total	80.0 ±11	69.8 ±18	0.03#
General	83.1 ±11.5	72.0 ±18.8	0.03#
Sleep/Rest	74.4 ±15	69.8 ±20.5	0.37#
Cognitive	91.7*(25)	70.8*(31.9)	0.041$

*(Median with IQR), # t -test, $ Man-Whitney Test

A significant association was found between failure to thrive and the child's perceived school domain ($r = –0.533$; $p = 0.013$) and overall ($r = –0.563$; $p = 0.008$) QoL score of the PedsQL scale. The history of sib death was associated with a poor get along score in the child ($r = –0.441$; $p = 0.045$), and salt-wasting variant kids reported poorer QoL in the cognitive fatigue domain ($r = –0.46$, $p = 0.03$). Higher parental education (graduate and postgraduate) correlated negatively with child reported sleep domain ($r = –0.57$, $p < 0.01$), total fatigue score ($r = –0.46$, $p = 0.02$) and parent-reported score in sleep fatigue domain ($r = –0.43$, $p = 0.02$). We also attempted to find the correlation between QoL scores in CAH cases with disease factors including age, Kuppuswami scale for socioeconomic status, the subtype of CAH, presence of ambiguous genitalia, precocious puberty, area of residence, change of sex, need for multiple OPD visits, admissions, stress dosing or surgeries, bone age, hydrocortisone dose, number of years of follow-up and 17-OHP levels, but could not find any of these to be significant in scores perceived by children nor by their parents.

Discussion

Assessment of QoL in chronic diseases is becoming standard of care to know the impact of illness and its therapy on patients' physical, mental, and social health. The various researchers studied QoL in CAH children using different questionnaires with varying results in different developed and developing world countries [2, 7, 8].

In our study, CAH children perceived lower QoL in the school domain on PedQL scale. Parent rated scores were lower in social, school, and total scores than healthy controls. Disease-related factors failure to thrive, CAH subtype, parental education, history of sibling death correlated significantly with poor core QoL.

A previous study from the US (mean age 8.2 [4.5] years) found no difference in self-reported core QoL scores in CAH children and controls, but parents reported lower scores in overall generic QoL (83.9 vs. 87.6), emotional (75.9 vs. 82.6), and school functioning (78.9 vs. 85.5) than controls. The authors suggested better glucocorticoid replacement using short-acting preparation and circadian rhythm to better QoL in their study [2]. However, Gilban *et al.* (mean age 11.4 years) found lower self-reported scores in physical (75.2 vs. 95.9), psychosocial (63.9 vs. 85.1), and overall (67.8 vs. 88.9) QoL when compared to controls. Parent-reported QoL was also significantly impaired in physical (43.7 ±8.0) and psychosocial (41.9 ±9.7) domains, but the study used a different tool (CHQ 50) from ours [7]. Yau *et al*. from Bangkok described poor QoL in all domains in self-reported scores, and parents in their study had lower scores in overall QoL score and emotional functioning. Poor compliance to therapy and lack of circadian rhythm in the replacement of glucocorticoids due to long-acting steroids such as prednisolone and dexamethasone were probable reasons for self-reported poor QoL in these studies than ours [9]. In a recent Indian study in 3–21 years CAH patients, children reported impaired QoL in school (77.8 vs. 84.1) and social (88.9 vs. 94.4) functioning. Parent-reported scores were significantly impaired in all domains, including the physical (76.9 vs. 93.9) and emotional (73.6 vs. 79.4) domains, which were spared in our study [10].

Compared to the West, our and previous Indian studies have reported lower scores in all PedQoL scale domains. The school QoL is worst impacted in both Indian and western settings [2, 7, 10]. The poor concentration, frequent school absenteeism due to hospital visits, hospital admission for disease crisis, and surgery may explain the same [2, 11]. The factors such as nonacceptance of the third gender in Indian society, lack of quality care from multidisciplinary experts, non-affordability of better disease monitoring biochemical markers (such as 17 hydroxyprogesterone, renin, aldosterone) are probable explanations for the poor quality of life in our study. Our study participants performed better in QoL than studies from Brazil and Bangkok due to use of shorter acting corticosteroids and round the clock replacement with eight hourly dosing schedules. Parents reported poor QoL in ours and all previous studies, which might be due to parent's worries regarding the impact of CAH on their child's future.

Adrenal insufficiency, primary or secondary, is associated with increased fatigue. Severe fatigue is associated with more psychological distress, functional impairment, less social functioning, decreased concentration, and physical activity. In our study, children had lower scores in general sleep areas of fatigue QoL scale, and parents felt their child is more tired in all domains of scale.

Giebels *et al*. reported severe fatigue in 42% of the CAH patients in their study cohort. Halper *et al*. showed no difference in fatigue perception except for sleep domain among children with CAH, but their parents reported more fatigue in all domains and the scale's overall score. The different explanations for normal and increased fatigue perceptions had been suggested. The lower normal fatigue perception at baseline and increased androgen level in CAH children are probable explanations proposed in previous studies for comparable scores to healthy children in most domains of fatigue scale. Poor physiological replacement of hydrocortisone increased nighttime cortisol and over perception of fatigue due to parents' feeling in chronic childhood illnesses explain the increased fatigue in ours and previous studies. But the enigma is still unresolved and needs further exploration [2, 12].

Some previous studies in children and adults reported negative association of QoL with disease factors such as sex, the subtype of CAH, bone age, age of diagnosis, adiposity, surgical intervention, hospitalizations, and emergency visits but some of the recent studies negate this association [2, 7, 8, 13–16].

The number of female patients is higher in ours as well as previous studies probably due to lack of newborn screening program and early death in male babies [8, 10]. Fatigue and QoL scores in males and females were similar in our study, corroborating Gilban and Halper's findings that the sex of the child is not a risk factor for the QoL [2, 7]. Some previous studies reported poor QoL in females due to genital ambiguity. Still, possibly the features of hyperandrogenism and genital ambiguity

alone are not a significant factor in QoL due to their younger age [8, 17]. However older girls, their parents and women have reported higher psychological, psychiatric, psychosexual, body image and poor reproductive outcome [16–18]. Similarly a recent systematic review has reported presence of psychological, sexual and impaired quality of life in males and stresses on their routine evaluation during follow up similar to female patients [19]. Failure to thrive correlated negatively with child perceived scores in the School QoL domain, Total QoL, and Cognitive Fatigue. This can be attributed to the fact that malnutrition in itself is known to be at risk of poor QoL and more fatigue [20, 21]. The child's age was negatively related to parent-reported school QoL. Children and parents are more worried as the age increases, and previous adult studies also report poor QoL in adults compared to children [13, 19, 22]. Parental education was associated with lower parent-reported scores in some domains, which can be explained by the fact that the more educated the parents, the more informed and worried they would be regarding the children's future, reflecting in their perception of child's QoL [2, 23, 24].

Comparison of QoL scores reported by children and their parents found no significant difference, but parents reported higher fatigue than their child (lower scores) in general, cognitive, and overall fatigue domains on Fatigue QoL scale. Halper found similar scores in the Core QoL scale, and the Fatigue Scale sleep domain score was different [2]. This finding decorates our approach of measuring QoL in children through their parents and multiple studies before ours [25–28].

The small sample size, lack of a local questionnaire for assessing cultural context are limitations for our study. Multicentric studies using indigenous and disease-specific questionnaires are required to find an accurate picture of QoL factors in children with CAH.

Conclusions

CAH affects core QoL and increases the fatigue perception in children. Children and parents have different perceptions of QoL, and parents are more worried than child. Hence, routine periodic assessment of QoL in CAH management will reveal unexpressed concerns of child and family and help deliver better clinical care and alleviate the worries.

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