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Quality of life in children and adolescents one-year after cure of Cushing syndrome: A prospective study

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Abstract

Objective—Cushing syndrome (CS) in children is associated with symptoms that may impair health related quality of life (HRQL). There are no prospective reports of HRQL in children with CS.

Methods—Prospective study of 40 children (mean age 13 ± 3.2 years) with CS evaluated prior to and one-year post-treatment. The Child Health Questionnaire (CHQ) was used to assess HRQL; Wechsler Intelligence Scale for Children (WASI) was used to assess cognitive function, and patient-reported symptoms were assessed with a CS symptom checklist.

Results—Active CS was associated with low physical and psychosocial summary scores compared to US population data ($p < 0.001$). Despite improvement from pre- to one-year post-cure, residual impairment remained in physical summary and function and scores, role-physical, global health, and emotional impact (parent). Incomplete recovery of adrenal function at one-year post-treatment was associated with impaired scores. WASI IQ scores declined and a correlation was noted between age at first evaluation and IQ score changes. Most self-reported CS symptoms showed improvement, but forgetfulness, unclear thinking, and decreased attention span did not improve after cure of CS.

Conclusion—CS in children and adolescents is associated with impaired HRQL, with residual impairment one-year after cure. Our results also suggest that younger children are more likely to experience negative changes in cognitive function. HRQL is an important outcome measure in children and adolescents with CS and identification of factors that contribute to HRQL may help to diminish the physical and psychological burden of disease in this population of patients.

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Keywords

Quality of life; Cushings; adrenal; pituitary; memory; cognitive function; paediatrics

Introduction

Chronic exposure to excess endogenous glucocorticoids in adults, children, and adolescents with Cushing syndrome (CS) is associated with detrimental health effects including truncal obesity, hypertension, insulin resistance, hyperglycaemia, impaired wound healing, hypercoagulability, osteoporosis, and gonadal dysfunction.¹ In adults, other problems associated with hypercortisolism include muscle weakness, fatigue, bone fractures, and cardiovascular events.^{2–4} In children, chronic exposure to excess endogenous glucocorticoids is also associated with suppression of linear growth.⁵ A long-term follow-up study of children and adolescents successfully treated for CS showed significant alterations in body composition, specifically a decrease in bone mass and an increase in visceral adiposity.⁶

It is well established that glucocorticoid excess also affects brain function. Studies of adult patients with CS report a high incidence of psychopathology, most commonly depression and/or major affective disorder; these symptoms gradually improve after correction of hypercortisolism and recovery of the hypothalamic-pituitary-adrenal (HPA) axis.⁷ Studies with adults have also reported cognitive impairment associated with glucocorticoid excess. We previously reported on cognitive and psychological function in children with CS and noted that exposure of children to excess endogenous glucocorticoids was associated with a decline in cognitive performance one-year after surgical cure. We did not identify any other psychopathology, at least not in the short term, and we did not study quality of life.^{8, 9}

Quality of life is an important outcome measure to assess the impact of chronic illness, as well as the effects of any treatment. Chronic illness has been reported to have an impact on the achievement of normal developmental tasks of childhood as well as the child's ability to perform activities of daily living and on overall family functioning. The Committee of Evaluation of Children's Health of the National Academies of Sciences and the Institute of Medicine define quality of life in paediatrics as the extent to which children are able (or enabled) to develop their potential, satisfy their needs, and develop their ability to interact successfully with their biological, physical, and social environments (<http://www.iom.edu/Object.File/Master/23/164/children'shealthfor%20WEB%20PDFonly.pdf>). Health-related quality of life (HRQL) measures include an assessment of the patient's sense of well-being, and physical, emotional, social, and intellectual function.

Limited information is available concerning the impact of CS and the effect of treatment on HRQL. A recent study in adults with CS¹⁰ reported overall improvement in HRQL measures one year after cure, however cross-sectional three year follow-up data showed residual impairment. There are no published studies on the effect of CS on HRQL measures in children. We sought to understand the nature and disease-specific impact of CS in children and adolescents on health related quality of life (HRQL) and conducted a prospective study using the Child Health Questionnaire (CHQ), cognitive function, and patient reported outcomes in a cohort of paediatric patients with CS (due to either pituitary or adrenal) before and one-year after surgical cure.

The hypothesis was that HRQL scores would improve after cure of CS; we also hypothesized that HRQL scores would correlate with measures of hypercortisolemia. We sought to determine whether variables such as recovery of the HPA axis, duration or degree of hypercortisolemia, or BMI affect HRQL outcomes since prior studies have shown a relationship between these

variables and HRQL measures. Prior studies have also reported that children may experience changes in cognitive function prior to and after cure of CS different than adults; therefore, we evaluated whether age was associated with change in cognitive function after cure of CS.^{8, 9, 11}

Subjects and methods

Protocol and subjects

Forty children with CS (22 females, mean age 13.1 ± 3.2 yrs, range 5 to 18 years) were evaluated prior to, and one-year post-treatment of CS: thirty-four children were diagnosed with pituitary tumours (Cushing's disease-CD) and underwent transsphenoidal surgery (TSS); six children had a diagnosis of adrenal tumours and underwent adrenalectomy (4 bilateral, 2 unilateral). The average duration of CS based on clinical symptoms and/or decreased growth velocity was 3 ± 1.6 years. All children were enrolled in protocols (95CH0059, 97CH0076 and 00CH160) approved by the institutional review board of the National Institute of Child Health and Human Development (NICHD) for evaluation and treatment of CS. The cause of CS was confirmed in all patients by histology.

Endocrine, cognitive, HRQL, and CS symptom assessments were done prior to, and one year post- transsphenoidal surgery (TSS) or adrenalectomy. Patients were invited to participate in the study prospectively and without knowledge of the eventual cure; all subjects were enrolled right after confirmation of CS by standard testing. Evaluation and confirmation of CS was performed as described by Batista *et al.*⁵ Participants were required to speak and read English and assent to this study. Only patients with biochemical evidence consistent with cure of CS were included in the final data analysis. Patients who did not complete all baseline and one-year follow-up HRQL assessments were not included; the design of the study was such that each patient served as his/her own control.

A total of 65 children confirmed to have CS were recruited from July 2000 to September 2006. Of the 65 children with confirmed CS, 40 completed HRQL data both pre and one- year post-treatment and were enrolled in the study. Patients ineligible for inclusion included: one patient with biochemical data not consistent with a cure of CS, nine patients with incomplete HRQL data (missing either pre or post-treatment HRQL data), one patient who declined to participate in HRQL and cognitive testing, and 14 non-English speaking patients (12 Spanish, 1 Portuguese, 1 French).

Health related quality of life measures

Child health questionnaire-parent report (CHQ) is a validated 50 item parent-reported measure of physical, emotional and psychological well-being of children and adolescents. It was also designed to assess the relative burden of disease and benefit of treatment and to detect clinically important changes over time. The CHQ measures physical (PhS) and psychosocial (PsS) health domains. Physical domains include: physical functioning, role/social functioning related to physical health, body pain/discomfort, and global health perception. Psychosocial domains include social limitations related to emotional-behavioural health, self-esteem, mental health, general behaviour, emotional impact (parent), and time impact (parent). Other domains measured include limitations in family activities and family cohesion. Domain scores range from 0 to 100, with higher scores indicating better HRQL. Summary scores for physical and psychosocial health are calculated with a mean of 50 (± 10). Normative data for US children are available and were used as a reference group for this study.¹²

Cognitive assessment

Cognitive assessment was completed for 26 of the 40 patients enrolled in the study prior to and one-year post cure of CS. Due to scheduling limitations cognitive assessments were not performed on 11 patients; 2 patients declined to participate in cognitive testing, and 1 patient was excluded because he received high dose glucocorticoids post-operatively to treat pseudotumor cerebri. The Wechsler Intelligence Scale for Children was administered to subjects below the age of 16 years (age at testing), whereas for adolescents (16 to 18 years at testing) the Wechsler Adult Intelligence Scale was used. All studies were conducted by a certified neuropsychologist, who was blind to the cause of CS and all aspects of the biochemical investigation. Both the adult and child version of the Wechsler Intelligence Scale are comprised of subscales, including verbal, performance, and full-scale IQ. The mean score for the WISC is 100 (± 15).^{13, 14} Higher scores on the WISC or WASI indicate better performance (This group comprises a different group of children than what was reported in our prior study⁸).

Patient- reported symptoms

Patients (or parent- proxy for children younger than 10 years old) were asked (pre- and post-treatment) to indicate whether they were currently experiencing any of the 34-items on a checklist pertaining to signs and symptoms associated with CS. This checklist was modified for paediatric use from a checklist that was used in studies of adults with CS.¹⁵

Statistical analysis

Descriptive statistics were calculated for continuous variables. Only patients who completed both pre- and postoperative responses on CHQ (n= 40) were included in the analysis. CHQ scores and all other data are reported as means, standard deviations (SD), and/or z scores (the latter when compared to the U.S. population normative data). Height SD units (Ht SDU), body mass index (BMI), and BMI SD units (BMISDU) were determined using anthropometric reference data for US children.¹⁶ Scores of CS patients at baseline and one year postoperatively were compared by the paired two-sided Student's *t*-test. Prior studies have reported that children may experience cognitive effects of endogenous hypercortisolemia that are different from adults with CS; therefore, we investigated whether age was associated with a change in IQ measures. One-way repeated measures ANOVA (with age at first evaluation as the covariate) and paired two-sided Student's *t*-test were performed to compare IQ scores pre- and post-treatment. Twenty-six of the 40 patients with complete HRQL data completed cognitive testing both pre and post-treatment and their results were included in the analysis. Repeated measures ANOVA was used to assess whether HPA axis recovery, degree and/or duration of hypercortisolism, or BMI were associated with scores on HRQL. Statistical significance was accepted for *p* values equal or below 0.05.

Results

Clinical evaluations pre- and postoperatively

At baseline, all patients had hypercortisolemia that was confirmed biochemically, as demonstrated by the group's lack of diurnal variation in serum cortisol levels (midnight cortisol, 557nmol/L $\pm$ 248; morning cortisol, 635 nmol/L $\pm$ 257) and their high urinary free cortisol (UFC) excretion (910 $\pm$ 950 nmol/24 hr; normal range 22 – 214 nmol/24 hr) (Table 1). The average duration of CS based on clinical symptoms and/or decreased growth velocity was 3 $\pm$ 1.6 years (range: 1 to 6 years). The average Ht SDU and BMI SDU improved from pre- to one-year post-cure. One year postoperatively, all patients showed biochemical and clinical evidence of cure of CS with normal UFCs (30 $\pm$ 30nmol/24 hrs); 21 patients (58.3%) had normalization of their HPA axis based on cortisol response of greater than 496 nmol/L 60 minutes after the intravenous administration of 250ug cosyntropin (Synacten®).

Post-operatively, patients with CD and the patient who had unilateral adrenalectomy, received glucocorticoid (GC) replacement calculated at a dose of 10–12mg/m²/day, divided twice a day, with a larger percentage of the total dose given in the morning, and a smaller percentage of the dose given in the late afternoon. Approximately four months post-operatively, patients were instructed to taper the dose, starting with the afternoon dose, and to reduce the dose every four to six weeks as tolerated. Patients who underwent bilateral adrenalectomy received GC replacement at a dose of 10 to 12mg/m²/day, divided two to three times a day. Fludrocortisone replacement was prescribed at a dose of 100mcg (daily).

At one-year follow-up 15 patients with CD had discontinued GC replacement, 10 patients had tapered the hydrocortisone dose to 5mg, 6 patients had minimally tapered the hydrocortisone dose to an average of 10mg a day (only two of these patients had adequate response to cosyntropin stimulation test), and 4 patients with panhypopituitarism were taking full GC replacement. For the two patients recovering from unilateral adrenalectomy, one was still on full replacement dose of hydrocortisone (15mg daily, with minimal response to cosyntropin stimulation test), and the other had discontinued hydrocortisone prior to the follow-up evaluation. Post-treatment assessment of anterior pituitary function included assessment of thyroid, gonadotropins, somatomedin, growth velocity, and pubertal status. Seven patients required thyroid hormone substitution, and 3 needed replacement for multiple pituitary hormones; 3 patients were receiving treatment to delay puberty with the intent to increase final height. IGF-1 levels in all patients were within the normal range (data not shown).

HRQL prior to and one year after surgical cure

Prior to treatment, parents reported significant limitations in their child's physical function, problems with performance of daily activity due to health, body pain, mental health, self-esteem, behaviour problems, and anxiety and concern, and impact on personal time due to their child's health problem. Physical and psychosocial summary z scores of patients with active CS were significantly lower than those of the US population norm ($p < 0.001$) (Figure 1).¹² Physical and psychosocial summary scores improved significantly from pre- to post-treatment ($p < 0.001$, $p < 0.049$, respectively).

The following scales showed significant improvement from pre- to post-treatment: mental health ($p < 0.006$), bodily pain ($p < 0.02$), self-esteem ($p < 0.01$), time-impact (parent) ($p < 0.04$) and were not significantly different from U.S. norms at post-treatment. Role emotional behaviour and behaviour scores were not significantly different from pre- to post-treatment

However, although the following scales showed significant improvement, at post-treatment scores of patients with CS remained significantly below US normative data for: physical function ($p < 0.001$), role-physical ($p < 0.02$), global health perception ($p < 0.001$), emotional impact (parent) ($p < 0.001$), and physical summary score ($p < 0.001$) (Table 2). Although we hypothesized that the degree or duration of hypercortisolemia might influence HRQL, we did not find an association between HRQL and duration of CS, pre-treatment UFC, or midnight plasma cortisol.

Cognitive evaluation

Twenty-six of the 40 patients enrolled in the study completed pre- and one-year follow-up cognitive testing. Verbal (113 ± 17 vs. 105 ± 16), performance (112 ± 12 vs. 101 ± 16) and full IQ (113 ± 15 vs. 103 ± 16) scores all declined post-treatment ($p < 0.001$) (lower scores indicate poorer performance). None of the pre-operative scores (active CS) showed deficits in cognitive function, in fact, the patients less than 14 years had verbal (VIQ), performance (PIQ), and full (FIQ) scores that were greater than one standard deviation above the mean. However, older age at first evaluation was associated with less deterioration in IQ scores from pre- to

post-treatment. Patients ≥ 14 years old showed a significant decline in VIQ ($p < 0.03$) but not in PIQ or FIQ from pre- to post-treatment. Patients < 14 years old had significant changes (deterioration) in all IQ measures from pre- to post-treatment ($p < 0.001$) (Table 3). There was a significant age-by-time effect for VIQ ($p < 0.005$), PIQ ($p < 0.001$), and FIQ ($p < 0.001$) measures, confirming that the magnitude of change was associated with age at first evaluation. The children in this study did not overlap with the children whose data was reported in our prior study of cognitive function in children with CD.⁸

Predictors of HRQL

One-year post treatment, incomplete recovery of the HPA axis (a post-Synachten® peak cortisol level of less than 496nmol/L) was associated with impairment of scores for physical function (85.6 ± 13 vs. 96 ± 0.5 ; $p < 0.008$); global health perception (51.6 ± 16.6 vs. 72.8 ± 0.4 ; $p < 0.001$); physical summary (44.2 ± 9.8 vs. 53 ± 0.3 ; $p < 0.004$); and emotional impact (parent) (58.4 ± 5 vs. 79.6 ± 0.6 ; $p < 0.001$) compared to gender-matched US norms. In addition, changes in pre- to post-treatment physical function scores (66.8 ± 28 vs. 87.2 ± 18) were associated with BMI (31.3 ± 9 vs. 25.8 ± 8.70) ($p < 0.05$) at 1 year post-treatment, consistent with findings from paediatric obesity studies of HRQL.^{17–19}

Patient reported symptoms

Patients (or parent- proxy for children less than 10 years of age) were asked to indicate whether they were experiencing any of the 34-items on a checklist pertaining to signs and symptoms associated with CS (Table 4). Pre-treatment, the most commonly reported symptoms related to physical health were weight gain (97.6%), round face (97.6%), headache (94.9%), bulging abdomen (92.7%), acne (92.3%), and fat pads around neck/shoulders (87.8%). The most commonly reported symptoms related to psychosocial health prior to treatment were fatigue (92.5%), mood swing (92.1%), increased irritability (87.2%), frustration (85%), feelings of being fat and ugly (82.5%), and anger (80%). One year post-treatment, symptoms related to physical health showed substantial improvement overall, although headaches remained a frequently occurring symptom (62.5%). Most symptoms related to psychosocial health showed improvement post-treatment, but fatigue remained common (67.4%). Symptoms of “forgetfulness” (41% vs. 57%), “unclear thinking” (41% vs. 42.5%), and decreased attention (37.5% vs. 51.2%) either did not improve or increased in frequency from pre- to post-treatment, which is consistent with the changes noted with the cognitive testing.

The majority of symptoms were reported more frequently in our paediatric patients than those previously reported in adults with Cushing syndrome. However, the self-reported symptom data from the adult patients represents a cross-sectional series, with patients deemed to be in postoperative clinical remission, with mean interval since treatment of 11.8 ± 4.9 years, which may explain why the overall frequency of reported active symptoms is lower in adult patients with CS post-treatment (Table 4).

Discussion

Our data show that children and adolescents with active CS had low physical and psychosocial summary scores compared to their peers in the US population consistent with similar data in adult patients with CS. One year after successful cure of CS, children and adolescents showed residual impairments in HRQL scores for physical summary scores, physical function, global health perception, role- physical, and emotional impact on parent.

These results are consistent with a recent long-term follow-up study by Van der Klaauw *et al.*²⁰ of disease specific impairments in HRQL in adults with pituitary adenomas, which reported that patients with CD experienced impairment in physical functioning compared to

patients surgically treated for non-functioning adenomas. In addition, Van der Klaauw *et al.*²⁰ reported that in comparison with other pituitary adenomas (acromegaly, prolactinoma, non-functioning), adult patients with CD had significantly more impairment in all areas of HRQL and experienced increased anxiety. It is important to note that Van der Klaauw *et al.*²⁰ and other studies of HRQL in patients with CS utilized generic health questionnaires, often in conjunction with assessment of mental state and/or cognitive function, which allowed comparison of general aspects of HRQL between various groups of patients but may not distinguish aspects of HRQL specific to CS. Recently, Webb *et al.*²¹ developed a disease-generated questionnaire to evaluate HRQL in adults with CS. This questionnaire was tested in 125 patients with either active or surgically treated CS in four countries. Results of initial testing with the questionnaire showed good reliability and validity as well as scores that correlated with relevant clinical parameters.²¹ Further testing of this questionnaire is needed to validate its utility in a larger adult patient population. In addition, adaptation of the questionnaire for use in children and adolescents would be beneficial.

In our paediatric patients, recovery of the HPA axis was associated with improvements in physical function, general health perception, emotional impact (parent), and in physical but not in psychosocial summary scores. A study by van Aken²² reported that hypopituitarism, which occurred in approximately half of the 58 subjects treated for CS, was an independent predictor of HRQL. In Lindsay's study (2006), hypopituitarism was not assessed biochemically, but patients who required glucocorticoid replacement after remission had marginally lower physical summary scores ($p=0.05$).¹⁰

Several secondary hormonal imbalances may also occur with chronic hypercortisolemia, which may affect HRQL. Several studies report that the time course for normalization of the HPA axis is typically nine to fourteen months;^{23–26} but how long it takes for all other hormonal axes to fully recover is largely unknown and could likely affect HRQL as suggested by Merke *et al.*⁶ This could also be true for other comorbidities.²⁷ A larger (and longer) study may be needed to delineate the potential impact of related comorbidities and their post-treatment course of recovery on HRQL of patients.

The effect of long-term exposure to elevated endogenous glucocorticoids on neurological function in the developing brain of children and adolescents is not known. The present data are consistent with our prior report that children with CS experienced a decline in cognitive function after cure of CS, despite reversal of cerebral atrophy.⁸ This is in contrast to studies of adults with CS, which reported that hypercortisolemia is associated with cognitive impairment and loss of brain volume that is partially reversible after eucortisolemia.^{7, 28–31} Interestingly, in our study, older age at time of initial evaluation was associated with less of a decline in cognitive function measures, which suggests that after a return to eucortisolemia the response of older adolescents may be more similar to adult CS patients.

It is unlikely that the residual deficit in HRQL measures was due to over-replacement with GC since 25 of the 32 patients, or 78% of the sample eligible to reduce GC (not counting 8 patients requiring full-replacement of GC due to bilateral adrenalectomy or panhypopituitarism) were either off GC completely, or on a dose of 5mg a day (16 patients were not taking any replacement GC at follow-up, 9 patients were taking 5mg of hydrocortisone, and 7 patients were taking an average hydrocortisone dose of 12mg). In addition, it is feasible that corticoid withdrawal syndrome may have been a contributing factor in the residual symptoms reported by patients. However, few studies adequately address this syndrome; but there are reports that symptoms of steroid withdrawal generally resolve over two to eight weeks so it is unlikely that this effect would be a factor one year after surgical cure and several months after most patients had tapered their GC replacement.^{32, 33}

In a study of adult patients with CS, Dorn *et al.*⁷ reported psychopathology in 66% of the subjects (mean age 36 ± 9 years, range 19 – 50 years) prior to treatment; 53.6% of the patients had residual problems at 3 months after surgical cure, 36 % at 6 months, and 24.1% at 12 months. We did not formally evaluate for psychopathology in our study; however parents completed a behaviour assessment questionnaire, which did not identify any psychopathology in this group of children and adolescents (data not shown). Dorn *et al.*⁷ did not evaluate cognitive function in their study of adult patients with CS.

We do not believe that mild GH deficiency, as the one that has been reported to persist up to one year postoperatively after TSS or adrenalectomy for Cushing syndrome⁹ could have played a role in the above results. All our patients had normal IGF-1 levels and experienced significant catch-up growth during the first post-operative year.

Children with CS are typically overweight or obese and prone to similar comorbidities including glucose intolerance and hyperlipidemia that may be associated with “healthy” obese or overweight children and adolescents. Prior quality of life studies in healthy obese adolescents report a significant relationship between BMI and general and physical health scales¹⁷. Overweight and obese adolescents were more likely to report functional limitations, while younger overweight and obese children were more likely to report a negative impact on self-esteem and school functioning. A study of HRQL in 110 overweight adolescents (BMI 41.7 ± 8.9 kg/m²) referred to an obesity treatment program reported significantly poorer scores on all areas except for role/social limitations (emotional, behavioural, and physical) and parent impact-time scales for obese adolescents compared to an age-matched non-overweight group.¹⁹ Although physical function scores for patients with CS significantly improved from pre- to post-treatment, results of our study show that BMI SDU at one-year post-treatment is a significant predictor of residual impairment on physical function scores.

HRQL is often used as an outcome measure of the burden of chronic medical conditions in children and adolescents. The literature on HRQL indicates that various chronic health conditions in childhood affect not only physical functioning but also emotional, social, and school functioning compared to healthy children.^{34–37} In our study headaches were frequently reported in children with CS prior to (94.9%) and one-year post-treatment (62.5%). Powers³⁶ reported a study of HRQL in a clinical sample of children with headaches (99% had clinical diagnosis of migraine, 40% had chronic daily headaches) and noted impaired HRQL for psychosocial health and school functioning subscales. Our study did not assess the subjective evaluation of disability related to headaches in children with CS. An assessment of the impact of headaches on HRQL in children with CS requires further investigation due to the high prevalence of this symptom both pre- and post-treatment.

Although this study of children showed there is overall improvement one-year after successful treatment, the residual effects of CS on HRQL measures were significant. The time and emotional-impact on parent scales are considered the most sensitive to both physical and psychosocial outcomes of children since chronic illness affects not only the patient, but also the entire family. In this series, residual impairment in emotional impact on parent scores was noted one-year post-treatment, which means that parents of children recovering from CS experience a great deal of emotional concern as a result of their child’s disease. A follow-up study to assess the long-term impact of CS on HRQL is underway to determine whether impairment in HRQL measures resolve within two to three years post-treatment.

The limitations of this study included the small number of subjects (which, however, was a large number for such a rare disease) and a single follow-up period at one-year post-treatment. However, this is the first ever report of HRQL measures in CS patients and the sample size was adequate to reveal significant differences both between pre- and post-treatment measures

as well as compared to a reference population at large. The small number of patients (and the large variation of individual values) was probably responsible for another finding: although one would expect that the degree or duration of illness may influence HRQL, we did not find an association between HRQL and duration of CS, pretreatment UFC, or midnight plasma cortisol. In addition, another possible explanation is that HRQL is a global assessment, whereas cortisol levels may fluctuate on a daily basis. Finally, differences in HRQL outcomes between patients with pituitary or adrenal CS were not evaluated in this series due to the small number of patients with adrenal causes of CS.

In conclusion, our findings demonstrate that children and adolescents affected by CS have impaired HRQL, which only partially resolves after successful treatment. Our results also suggest that younger children are more likely to experience negative changes in cognitive function from pre- to post-treatment, although all post-treatment IQ scores remained within a normal range (except for one child). HRQL is an important outcome measure in children and adolescents with chronic medical conditions such as CS, and may be a useful tool in the assessment of remission status in the post-operative period. Identification of additional factors that contribute to HRQL may help to diminish the physical and psychological burden of disease in this population of patients.

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Figure 1.

Individual CHQ domain z scores baseline (pre) and 1-yr after (post) treatment in 40 children with CS treated with either TSS or adrenalectomy. Results are expressed as z scores compared to age-matched normative data from the US population. The CHQ domains represented are those that showed significant improvement from pre- to post-treatment and include: physical summary score (PhS), physical function (PF), role-physical (RP), global health (GHP) (note: GHP was the only score that declined from pre- to post- treatment), emotional impact on parent (PE), mental health (MH), bodily pain (BP), self esteem (SE), time impact- parent (PT), and psychosocial summary score (PsS). $p < 0.05$ for differences between all domains and US norms pre-treatment, $p < 0.01$ for differences between PhS, PF, RP, GHP, and PE post-treatment scores and US norms.

Table 1
 Characteristics of children with Cushing syndrome at baseline and one-year after surgical cure

Females (%)	55%	Unilateral adrenal tumor	2
Pituitary CS	34	Bilateral micronodular disease	4
	Baseline	Postoperative evaluation (1 year)	
Age (yr)	13.3 ± 3 yrs	14.5 ± 3.3yrs	
Height (SDS)	-1 ± 1.4	-0.8 ± 1.3	
BMI (SDS)	2 ± 0.7	1.1 ± 1	
24hr urine free cortisol (reference 22– 214 nmol/24hr)	910 ± 950 nmol/24hr	30 ± 30 nmol/24hr	

Table 2CHQ mean ($\pm$ sd) scores in 40 patients prior to and one- year after cure of CS

	Pre-tx CS	Post-tx CS	Pre- vs. post-Rx (<i>p</i> value)
Physical summary score	37.2 ($\pm$ 15.8)	47 ($\pm$ 11)	<0.001
Psychosocial summary score	45.2 ($\pm$ 7.8)	49.2 ($\pm$ 10)	<0.049
Physical function	66.9 ($\pm$ 28)	87.2 ($\pm$ 18.1)	<0.001
Role physical	70.3 ($\pm$ 37)	86.3 ($\pm$ 27.8)	<0.01
Global health perception	64.6 ($\pm$ 20)	58 ($\pm$ 16.8)	<0.14
Bodily pain	56.1 ($\pm$ 29.2)	77.1 ($\pm$ 23.6)	<0.001
Role-emotional/behavior	85.9 ($\pm$ 22.3)	87.4 ($\pm$ 25.4)	<0.82
Parent-impact-time	72.2 ($\pm$ 25.8)	84.7 ($\pm$ 22.3)	<0.02
Parent-impact-emotional	40.1 ($\pm$ 22.5)	63.8 ($\pm$ 25)	<0.001
Self-esteem	61.7 ($\pm$ 18.7)	71 ($\pm$ 22.7)	<0.001
Mental health	67.2 ($\pm$ 16)	76.4 ($\pm$ 14.6)	<0.012
Behaviour	80.8 ($\pm$ 16.5)	75.2 ($\pm$ 18)	<0.25

Table 3
Weschler IQ scores: pre- post- treatment: all patients & subgroups by age at first evaluation (mean $\pm$ SD)

		Verbal IQ	Performance IQ	Full IQ
All patients (n=26)	Pre- tx	112.1 $\pm$ 17	112.1 $\pm$ 13	112.9 $\pm$ 15
	Post- tx	104.8 $\pm$ 16 *	100 $\pm$ 15 *	102.9 $\pm$ 15 *
Patients $\geq$ 14 years (n= 11)	Pre- tx	99.5 $\pm$ 15	102.5 $\pm$ 10	100.5 $\pm$ 12
	Post- tx	76.3 $\pm$ 15 ‡	100.8 $\pm$ 17 (p NS)	98.5 $\pm$ 16 (p NS)
Patients < 14 years (n=15)	Pre- tx	121.3 $\pm$ 11	119.1 $\pm$ 9	122.1 $\pm$ 9
	Post- tx	111 $\pm$ 15 *	99.4 $\pm$ 14 *	106.1 $\pm$ 14 *

*
p < 0.001

‡
p < 0.03

Table 4

Prevalence of symptoms associated with active CS and one- year post- cure in children and adolescents (n= 40) and comparison to CS adult patients ¹⁵.

Symptoms	% of patients with symptoms		
	Prior to treatment (n= 40)	1-yr post-treatment (n=40)	Adults post-treatment (n=343;cross-sectional data)
Weight gain	97.6	34.1	30.4
Round face	97.6	19.5	8.1
Headache	94.9	62.5	--
Bulging abdomen	92.7	21.9	29.3
Fatigue	92.5	67.4	41.3
Acne	92.3	36.6	7.2
Mood swings	92.1	42.8	27.4
Fat pad neck/shoulder	87.8	20	9
Increased irritability	87.2	39	21.3
Feelings of frustration	85	63.4	23.1
Feeling of being fat & ugly	82.5	36.5	21.6
Ruddy or red complexion	81.6	19.5	10.5
Anger	80	52.3	15.6
Decreased muscle strength	76.9	43.9	30.4
Feelings of sadness	76.9	39	27.6
Facial hair	75	46.1	27.6
Purple stretch marks	72.5	29.3	13.5
Irregular menses	70.6	35.9	11.3
Trouble sleeping	70	40	33.3
Bruise easy	69.2	28.6	24.3
Decreased ability to exercise	66.7	35	27
Temper outbursts	66.7	31	16.5
High blood pressure	59	12.5	25.2
Anxiety	57.5	32.5	28.4
Depression	56.4	35.9	31.2
Crying spells	55	24.4	16.5
Indecision	52.6	26.7	15.6
Thinning or balding of hair	50	27.5	21
Feelings of hopelessness	47.5	12.5	15.9
Increased nervousness	43.9	18.9	15.6
Forgetfulness	41	57	35.7
Unclear thinking	41	42.5	19.5
Decreased attention span	37.5	51.2	24.6
Hand tremors	36	20	--
High blood sugar	30.8	8.2	10.5
Unable to work/attend school	25.6	26.1	16.8
Feelings of "being left out"	7.3	7.3	9.3