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Pediatric Cushing Disease: Disparities in Disease Severity and Outcomes in the Hispanic and African American Populations

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Abstract

Background—Little is known about the contribution of racial and socioeconomic disparities to severity and outcomes for children with Cushing disease (CD).

Methods—129 children with CD, 45 Hispanic/Latino or African American (HI/AA) and 84 non-Hispanic White (non-HW), are included. A 10-point index for rating severity (CD-severity) incorporated degree of hypercortisolemia, glucose tolerance, hypertension, anthropomorphic measurements, disease duration, and tumor characteristics. Race, ethnicity, age, gender, local obesity prevalence, estimated median income, and access to care were assessed in regression analyses of CD-severity.

Results—The mean CD-severity for the HI/AA group was worse than the non-HW group (4.9 ± 2.0 vs 4.1 ± 1.9, p = 0.023); driving factors included higher cortisol levels and larger tumor size. Multiple regression models confirmed that race (p=0.027) and older age (p=0.014) were the most important predictors of worse CD-severity. When followed up a median of 2.3 years after surgery, the relative risk of persistent CD combined with recurrence was 2.8 times higher in HI/AA compared to non-HW (95% CI: 1.2–6.5).
Conclusions—Our data show that the driving forces for the discrepancy in severity of CD are older age and race/ethnicity. Importantly, risk of persistent and recurrent CD was higher in minority children.

Introduction

An estimated 1 to 1.5 per million children are affected a year by Cushing syndrome; of those 75–80% are caused by an adrenocorticotropic hormone (ACTH) secreting pituitary tumor (Cushing disease, CD) (1). Prolonged exposure to excess glucocorticoids leads to obesity, growth deceleration, striae, muscle weakness, and hypertension, impaired glucose intolerance, osteopenia/osteoporosis, and alterations in cognitive function and mood (2). These tumors are typically benign and early identification and surgical resection may lead to long-term remission and cure (3). Importantly, improved outcomes in children with CD are associated with younger age at surgery, smaller adenomas and lack of dural invasion (3).

Racial, ethnic, and socioeconomic disparities have been investigated in a number of diseases associated with tumors; significant differences in disease incidence, prevalence, and mortality have been identified (4–6). Even as treatment and detection of tumors have improved, African-Americans continue to experience lower survival rates than whites for all cancers (7). For the most common childhood cancer, acute lymphoblastic leukemia, Black, and Hispanic children have worse survival than white children; in addition, SES is associated with poor survival in childhood leukemia (8,9). 5-year survival rates among Hispanics (HI) (74%) and African American (AA) (75%) children remains poorer than that among non-Hispanic Whites (non-HW) (85%) for CNS malignancies as well as for many other tumors (5,10). While disproportionate morbidity and mortality have been shown for more common cancers, no prior studies have examined differences in severity of presentation for children with CD. In addition to looking at individual clinical parameters and comparing them between racial groups, we also introduced a combined pediatric CD severity score (CD-severity) as a tool for research purposes. As has been done in other disease states when severity scores are formulated, we looked at the comorbidities associated with CD. Each of the individual factors used in the scoring system has independently been associated with an increased risk of a poor outcome for patients (degree of hypercortisolemia, impaired glucose tolerance, hypertension, height impairment BMI, delay in diagnosis, and larger tumor (3,11,12)). Our severity score aims to quantify the magnitude of glucocorticoid exposure in order to characterize the severity of illness. In addition, inhibition of linear growth by exogenous steroids has been shown to be dose-dependent, a unique factor in children vs. adults with CD. In adults with CD, hypertension and diabetes are known to be the main determinants of cardiovascular events and mortality; we wanted to capture these signs in children as important determinants of overall disease severity (13–16). In the current study, we examined data to assess CD-severity at presentation and risk of persistent disease and/or relapse.
Methods

Subjects

Patients with CD ≤ 18 years at the time of transphenoidal surgery (TSS) were consecutively treated at the National Institutes of Health Clinical Center (NIH CC) from January 1, 1997 through January 1, 2015. Informed consent and assent was obtained in all patients. The Institutional Review Boards of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) NIH, approved the research protocol (Clinical Trial Registration number: NCT00001595)

Study Design

Patients were admitted for pre-operative testing within 1 month of their surgical date to confirm CD following a standardized protocol. A venous sampling catheter was placed at least 2 hours before the test; cortisol and ACTH levels were drawn at 23:30 and 24:00, these values were averaged to become the “Average” late night cortisol value. Preoperative evaluation included: 1) 24-hour urinary free cortisol (24-h UFCs), 2) average late night (23:30 h, 24:00 h) and morning (07:30 h, 08:00 h) serum cortisol levels, as well as 3) average morning (7:30 h, 8:00 h) plasma ACTH levels. The initial visit data included the age at surgery, gender, race/ethnicity (by self-report), number of TSS, years of hypercortisolism (as determined by review of growth chart and age of crossing percentiles for height and weight, as well as self-report of onset of physical symptoms of CD) height, height z-score, weight, body mass index (BMI), BMI z-score. BMI (kilogram per meter squared) and BMI – for –age z-scores were calculated from the Centers for Disease Control and Prevention (CDC) growth charts (17). Surgical outcome, length of follow up, as well as rates of recurrent CD were collected. A 10-point index for rating severity in pediatric CD (CD-severity) (Table 1) was devised based on review of the most clinically relevant manifestations in children, the co-morbidities associated with CD, and the independent association of each factor with risk of a poor clinical outcome. Seven clinical features were selected on the basis of their frequency and importance. Degree of hypercortisolemia, impaired glucose tolerance, and hypertension were graded on an ordinal 3-point scale (0–2) with pre-defined cut-offs based on severity. Height and BMI z-scores, duration of disease, tumor size, and presence of tumor invasion were graded on an ordinal 2-point scale (0–1). Total severity scores ranged from 0–10. Estimated income data was obtained from US Census and World Bank databases, using zip codes of residence for US census data (18,19). Prevalence of obesity in children by state was extrapolated from the Data Resource Center for Child and Adolescent Health, a project of the Child and Adolescent Health Measurement Initiative (CAHMI-2011) where obese children with BMI z-score ≥95% ile are reported by state (Table 2) (20). Access to pediatric endocrinologists by state was based on the relative distribution of American Board of Pediatrics certified Pediatric Endocrinology Diplomates by state as of 12/31/2012 (Table 2) (21). Status of country in terms of whether or not it is developed was based on the International Monetary Fund’s World Economic Outlook Report, April 2015 (22).
Data Analysis

Results were described as frequencies and percentages, or means and standard deviations, unless otherwise indicated. Groups were defined based on self-reported racial and ethnic descriptions, and were categorized as Hispanic/Latino or African American (HI/AA) if they indicated Hispanic or Latino ethnicity or indicated Black/African American race regardless of ethnicity. The non-Hispanic white (non-HW) category consisted of those that indicated not Hispanic or Latino for ethnicity and white for race. Those not meeting these definitions were excluded. Data were assessed for their distributions and log-transformed as necessary. Continuous data were compared using the two-sample t-test or Wilcoxon rank-sum test, as applicable; categorical data were compared by the chi-square or Fisher’s exact test, and Kruskal-Wallis test was used for singly ordered categories. Simple and multiple regression analyses were carried out to assess the relation between explanatory variables (race/ethnicity, age, gender, prevalence of obesity in children by state, estimated median income per zip-code, access to pediatric endocrinologists, and whether an individual resided in a developing country) and disease severity outcome as scored by the index described above. The Kaplan-Meier method was used to compute the survivor function for time to recurrence that were compared between the two groups using the log-rank test. Data were considered statistically significant if the resulting p-value was less than 0.05, or the relative risk (RR) 95% Confidence Interval (CI) excluded 1.0. Corrected p-values are reported for post-hoc comparisons which utilized the Bonferroni method. Analyses were done using SAS v9.4 (SAS Institute, Inc., Cary, NC).

Results

From an initial population of 139 pediatric CD patients admitted to the National Institutes of Health Clinical Center (NIH CC) between the years 1997–2015, data were collected retrospectively from records of children diagnosed with CD at age ≤8 years (64 females, 65 males, median age 13.4 years). The year 1997 coincided with the initiation of our protocol entitled “A Clinical and Genetic Investigation of Pituitary Tumors and Related Hypothalamic Disorders,” in which these patients were enrolled, as well as they year that standardization of racial and ethnic designations were revised by the Office of Management and Budget (23). Patient racial/ethnic groups were distributed as 34.9% (n=45) HI/AA and 65.1% (n=84) non-HW. Asian patients (n=6) and those with unknown race/ethnicity (n=4) were excluded from the study; thus, a total of 129 patients were included in the analysis. The complete datasets, stratified by race/ethnicity showing both HI, AA, and non-HW data individually as well as HI and AA grouped together, are shown in Tables 2 and 3.

Median income was higher in the non-HW group and fewer from the non-HW group were from developing countries (both p<0.001; Table 2) than the HI/AA group. The developing countries where our patients reside, followed by the number of patients from each country: Peru (5), Chile (4) Brazil (3), and one child each from Colombia, Ecuador, Guatemala, Venezuela, Uruguay, and Argentina.

Midnight cortisol was higher in the HI/AA group (23.3 ± 22.0 μg/dL vs 16.2 ± 8.5 μg/dL, p=0.040), and height SDS score was more severely affected (−1.6 ± 1.2 vs −1.1 ± 1.1,
p=0.022), than non-HW. Tumor size was also larger in HI/AA (6.3 ± 7.1 mm vs 3.2 ± 3.3 mm, p=0.007).

The mean CD-severity score for HI/AA was worse than for the non-HW group (4.9 ± 2.0 vs 4.1 ± 1.9, p=0.023). Simple regression analysis of disease severity revealed that age was an independent explanatory variable of disease severity as measured by CD-severity (r_p=0.23, p=0.008), while gender, number of pediatric endocrinologists per capita, median income, prevalence of obesity in the patient’s state of residence, and whether or not an individual resided in a developing country were not independent driving factors. Considering these effects together in multiple regression models confirmed that race (p=0.027) and older age (p=0.014) were the most important predictors of worse CD-severity.

Follow up

Of the 129 children in this study, 124 achieved remission after surgery. Of the 5 patients who did not achieve remission after surgery, two then underwent radiation therapy and three were managed with ketoconazole. Long-term follow up was available in 112 patients (87%) with mean postoperative follow up 45.5 ± 39.9 months, median follow up 27.9 months (IQR=13.2–68.7 months), range 1.4–158.7 months. Interestingly, follow up was available in more non-HW individuals, 78/84 (93%) as compared to 34/45 (76%) of HI/AA individuals (p=0.012), and mean CD-severity was significantly worse in those individuals without long-term follow up (5.4 ± 1.7 vs 4.2 ± 2.0, p=0.017). Thirteen of the 108 patients with long term follow up (excluding those who had persistent disease) developed recurrent CD over the course of the study, with a mean time to recurrence 49.2 ± 28.2 months, range 1.9 to 111.3 months. Of these individuals, one underwent bilateral adrenalectomy, three were treated with pituitary radiation therapy, two underwent repeat pituitary surgery in addition to pituitary radiation therapy, six underwent repeat TSS alone, and one individual is awaiting repeat surgery. Two individuals are currently deceased, one secondary to suicide and another from pulmonary embolism. Overall, 13 patients had recurrence of disease after surgery and 5 had persistent disease after surgery. As expected, CD-severity was worse among those individuals with recurrent disease (5.1 ± 1.7 vs. 4.1 ± 1.9, p=0.041). Among those individuals with long term follow up or known persistence of disease after surgery, a higher proportion of individuals in the HI/AA group had lack of initial cure or recurrence (10 out of 35 AA/HI, 28.6%) when compared to non-HW (8 out of 78, 10.3%, p=0.024). The relative risk of persistent CD combined with recurrence was 2.8 times higher in HI/AA as compared to non-HW (95% CI: 1.2–6.5). When disease free survival is compared (time in remission), the median for HI/AA 26.8 (95% CI: 13.2–50.3) months vs. non-HW 34.8 (95% CI: 19.7–60.1) months; log-rank p=0.028 (Figure 1).

Discussion

Our findings show disproportionately higher severity of CD in the HI/AA patients both preoperatively and postoperatively. SES was also lower in the HI/AA individuals. SES status contributes to health disparities as poverty, lack of health insurance, and poor access to care cause the medically underserved to bear a greater burden of disease than the general population. In the United States, both African American and Hispanic/Latino minority
groups have lower SES, decreased access to healthcare, and worse outcomes across a
number of health indicators compared to whites (24). For all cancer sites combined,
residents of poorer countries have higher death rates from cancer compared to more affluent
countries (25). Later stage at diagnosis of cancer has been associated with lower SES (6). It
follows that the HI/AA children in our study had a higher proportion diagnosis at an
advanced stage; children of low-income families may have limited access to specialized care
and cancer diagnosis, including CD, may be delayed (26,27).

One potential cause for worse CD-severity scores in the HI/AA group may be the higher
prevalence of obesity in minority children, which may lead practitioners to overlook one of
the presenting symptoms of CD. Obesity prevalence for non-Hispanic white youth and
young adults is 14.1%, while the prevalence for Hispanic/Latinos and African Americans is
22.4% and 20.2%, respectively (28). In addition, delayed referral for surgical intervention or
participation in a clinical trial for a rare disease may be contributing factors for the higher
severity in the HI/AA children with CD. TSS is the treatment of choice with optimal
outcomes when performed at tertiary referral centers (1). Racial and socioeconomic
disparities have been found specifically for children in terms of access to high-volume
neurooncological care (29). In addition, minorities with cancer are underrepresented in
pediatric oncology research protocols (30).

Social factors including race/ethnicity, educational level, language/culture barriers, income,
poverty, unemployment, and lack of health insurance all contribute to health outcomes, in
addition to one’s genetic background (10,25). Progress in pediatric cancer survival rates is
highly attributable to early detection and advances in therapeutic protocols, and patients’
participation in clinical trials (7). The association of younger age, smaller tumor size, and
absence of cavernous sinus invasion (experienced surgeon and center of referral) with lasting
biochemical remission suggests that earlier diagnosis when the tumor is small and non-
invasive will enhance long term outcome; late pituitary CD diagnoses are associated with
more comorbidities and higher recurrence and mortality rates (3). Awareness of the signs
and symptoms of CD needs to be increased among care providers. We suggest the American
Cancer Society (ACS) and ACS Cancer Action Network together should influence public
policies and promote patient’s navigators and medical homes in order to reduce health
disparities (31–33).

Our study is the first to introduce a combined severity score for childhood CD, which we
observed to be associated with outcome; that is, the higher the severity score, the higher the
likelihood of recurrence and failure to cure. One limitation of our study associated with the
use of a novel severity score for pediatric CD is that it has yet to be validated in a larger
cohort. Given the rarity of childhood CD, we will work towards collaborating with other
institutions to validate the performance of the severity scoring system. Another limitation of
our study is the use of residential zip codes as a proxy for income that may not account for
within-area variation. In addition, patient health insurance status is not collected at the NIH
Clinical Center as patients are participating in a research study.

HI/AA children had comparatively more severe disease presentation of CD compared with
non-HW, and a nearly three-fold higher risk of persistent CD or recurrent disease after
surgery. Our data show that the driving forces for the discrepancy in disease severity are older age at time of treatment and race. Delayed diagnosis and treatment and lack of access to care for these underserved children may contribute to presentation at a later age and increased morbidity. We speculate that delayed diagnosis and treatment, barriers to access to medical care, and poorer quality health care for these underserved patients may contribute to presentation at a later age and increased morbidity. Additional research is needed to identify potential modifiable factors that may improve care for these patients.

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Figure 1.
The Kaplan-Meier curves for disease free survival in HI/AA and non-HW study groups (time in remission) HI/AA median=26.8 (95% CI: 13.2–50.3) months vs. non-HW median=34.8 (95% CI: 19.7–60.1) months; log-rank p=0.028.
Table 1

Cushing Disease Severity Score

| Severity Score Component | To capture | Cut-off | Component Score |
|--------------------------|------------|---------|-----------------|
| S1                       | Degree of hypercortisolemia | MSC &/or 24h-UFC < 50% ile | 0 |
|                          |            | MSC &/or 24h-UFC ≥50% ile – < 75% ile | 1 |
|                          |            | MSC &/or 24h-UFC ≥75% ile | 2 |
| S2                       | IGT        | FPG < 100 mg/dL | 0 |
|                          |            | FPG ≥100 mg/dL | 1 |
|                          |            | FPG ≥126 mg/dL &/or DM-Dx | 2 |
| S3                       | Hypertension | SBP & DBP z-score both < 2 | 0 |
|                          |            | SBP or DBP z-score ≥2 | 1 |
|                          |            | HTN-Tx | 2 |
| S4                       | Height z-score | Height z-score > −0.5 | 0 |
|                          |            | Height z-score ≤ −0.5 | 1 |
| S5                       | BMI z-score | BMI z-score < 2 | 0 |
|                          |            | BMI z-score ≥2 | 1 |
| S6                       | t (to diagnosis) | < 3 years | 0 |
|                          |            | ≥3 years | 1 |
| S7                       | Tumor characteristics (size & invasion) | Adenoma size < 5 mm | 0 |
|                          |            | Adenoma size ≥5 mm &/or CS invasion | 1 |

Abbreviations: MSC= Midnight Serum Cortisol, 24h-UFC= 24 hour Urine Free Cortisol, IGT= Impaired Glucose Tolerance, FPG= Fasting Plasma Glucose, DM= Diabetes Mellitus, DM-Dx= Diabetes Mellitus Diagnosis, DM-Tx= Diabetes Mellitus treatment with insulin or metformin at diagnosis, BP z-score= Blood Pressure z-score, SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure, HTN-Tx= On medication for hypertension at diagnosis, BMI= Body Mass Index, t (to diagnosis)= Duration from first symptoms to diagnosis, CS= cavernous sinus.

SI conversion factors: To convert fasting plasma glucose to mmol/L, multiply values by 0.0555.

CD Severity Score = sum of S1–S7
Table 2

Demographic characteristics of 129 children with Cushing Disease, stratified by race/ethnicity.

| Variable                        | Hispanic (n = 36) | African American (n = 9) | Non-Hispanic White (n = 84) | Hispanic or African American (n = 45) | P-value\(^1\) | Hispanic or African American (n = 45) | P-value\(^2\) |
|--------------------------------|------------------|-------------------------|-----------------------------|--------------------------------------|-------------|--------------------------------------|-------------|
| Age (years)                    | 13.4 ± 3.5       | 13.8 ± 2.2              | 12.9 ± 3.2                  | 13.5 ± 3.3                           | 0.61        |                                      | 0.34        |
| BMI z-score                    | 1.9 ± 0.8        | 2.4 ± 0.4               | 2.1 ± 0.7                   | 2.0 ± 0.8                            | 0.25        |                                      | 0.64        |
| Height z-score                 | −1.4 ± 1.2       | −2.0 ± 1.1              | −1.1 ± 1.1                  | −1.6 ± 1.2                           | 0.030 \(^*\)  |                                      | 0.022 \(^*\) |
| Gender (F)                     | 21 (58%)         | 3 (33%)                 | 40 (48%)                    | 35 (78%)                             | 0.35        |                                      | 0.58        |
| Median income                  | $29,406 ± $36,034| $66,128 ± $34,935       | $59,231 ± $31,314           | $37,466 ± $38,564                    | <0.001 \(^*\)   |                                      | <0.001 \(^**\) |
| Prevalence of obesity in resident state\(^a\) |                     |                         |                             |                                      |             |                                      |             |
| ≥20.1%                         | 0                | 1 (11.1%)               | 9 (12.3%)                   | 11 (24.4%)                           | 0.63        | 1 (4.6%)                             | 0.76        |
| 15.1%–20%                      | 3 (23.1%)        | 4 (44.4%)               | 22 (30.1%)                  | 27 (59.5%)                           |             |                                      |             |
| 10.1%–15%                      | 10 (76.9%)       | 4 (44.4%)               | 37 (50.7%)                  | 37 (80.8%)                           |             |                                      |             |
| 5.1%–10%                       | 0                | 0                       | 5 (6.9%)                    | 0                                    | 0.29        | 3 (7.8%)                             | 0.097       |
| 0%–5%                          | 0                | 0                       | 0                           |                                      |             |                                      |             |
| Pediatric endocrinologist per-capita score\(^b\) | 3.9 ± 1.0        | 3.6 ± 1.5               | 3.3 ± 1.2                   | 3.7 ± 1.2                            | 0.29        |                                      | 0.097       |
| Individuals from a developing country | 18 (50%)         | 0                       | 3 (3.6%)                    | 18 (40.0%)                           | <0.001 \(^*\)   |                                      | <0.001 \(^**\) |

Data are mean ± standard deviation or frequency (percent). Sums may not add up to total numbers due to missing or not applicable (ie, state information for non-US patients) data.

\(P\)-Values: 1: Comparing all three groups; 2: Comparing combined Hispanic or African American to Non-Hispanic White.

\(^a\)Percentage of children with BMI z-score at ≥95% ile for each patient’s resident US state, scores of 1–5 correspond as follows: 1 (≥20.1%), 2 (15.1%–20%), 3 (10.1%–15%), 4 (5.1%–10%), 5 (0%–5%).

\(^b\)Pediatric endocrinologists per-capita score for each patient’s resident US state: 0 (no certified specialists), 1 (1:150,000+), 2 (1:100,000–149,000), 3 (1:75,000–99,999), 4 (1:50,000–74,999), 5 (1:1–49,999).

\(^c\)Post-hoc corrected \(p=0.011\) for Hispanic vs African American and \(p<0.001\) for Hispanic vs Non-Hispanic White.

\(^d\)Post-hoc corrected \(p=0.013\) for Hispanic vs African American and \(p<0.001\) for Hispanic vs Non-Hispanic White.

Abbreviations: BMI = Body Mass Index; US = United States, F= female.
Table 3

Patient characteristics of 129 children with Cushing Disease as they relate to severity of presentation, stratified by race/ethnicity.

| Variable                  | Hispanic (n=36) | African American (n=9) | Non-Hispanic White (n=84) | P-value\(^1\) | Hispanic or African American (n=45) | P-value\(^2\) |
|---------------------------|-----------------|------------------------|---------------------------|--------------|-----------------------------------|--------------|
| MSC (µg/dL)               | 25.1 ± 23.9     | 16.1 ± 10.3            | 16.2 ± 8.5                | 0.038 \(^a\) | 23.3 ± 22.0                      | 0.040 \(^*\) |
| 24h-UFC (µg/24h)          | 905.3 ± 2,561.1 | 453.5 ± 612.2          | 263.4 ± 237.7             | 0.21         | 815.0 ± 2,306.3                  | 0.13         |
| Adenoma size (mm)         | 6.0 ± 6.7       | 7.4 ± 8.9              | 3.2 ± 3.3                 | 0.025 \(^b\) | 6.3 ± 7.1                        | 0.007 \(^*\) |
| CS Invasion               | 4 (11.1%)       | 1 (11.1%)              | 3 (3.6%)                  | 0.22         | 5 (11.1%)                        | 0.13         |
| DM-Tx                     | 6 (16.7%)       | 1 (11.1%)              | 4 (4.8%)                  | 0.087        | 7 (15.6%)                        | 0.049 \(^*\) |
| HTN-Tx                    | 9 (25.0%)       | 3 (33.3%)              | 12 (14.3%)                | 0.17         | 12 (26.7%)                       | 0.10         |
| t (to diagnosis) (years)  | 2.8 ± 2.1       | 4.2 ± 2.3              | 2.5 ± 1.5                 | 0.089        | 3.1 ± 2.2                        | 0.37         |
| CD-severity score (0–10)  | 4.6 ± 1.8       | 6.0 ± 2.5              | 4.1 ± 1.9                 | 0.012 \(^c\) | 4.9 ± 2.0                        | 0.023 \(^*\) |

Data are mean ± standard deviation or frequency (percent).

P-values: 1: Comparing all three groups; 2: Comparing combined Hispanic or African American to Non-Hispanic White.

\(^a\) = post-hoc corrected p=0.040 for Hispanic vs Non-Hispanic White,

\(^b\) = post-hoc corrected p=0.041 for Hispanic vs Non-Hispanic White,

\(^c\) = post-hoc corrected p=0.014 for African American vs Non-Hispanic White.

Abbreviations: MSC= Midnight Serum Cortisol, 24h-UFC= 24 hour Urine Free Cortisol, CS Invasion= Invasion of cavernous sinus, DM-Tx= Diabetes Mellitus treatment with insulin or metformin at diagnosis, HTN-Tx= On treatment for hypertension at diagnosis, t (to diagnosis)= Duration from symptoms to diagnosis, CD= Cushing Disease, SI conversion factors: To convert midnight cortisol to nmol/L, multiply values by 27.588.

To convert 24h-Urinary free cortisol (µg/24h) to nmol/24h multiply values by 2.76 (molecular weight= 362.5).