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Pediatric Cushing disease: disparities in disease severity and outcomes in the Hispanic and African-American populations

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BACKGROUND: Little is known about the contribution of racial and socioeconomic disparities to severity and outcomes in children with Cushing disease (CD).

METHODS: A total of 129 children with CD, 45 Hispanic/Latino or African-American (HI/AA) and 84 non-Hispanic White (non-HW), were included in this study. A 10-point index for rating severity (CD severity) incorporated the 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 in the HI/AA group was worse than that in 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 for persistent CD combined with recurrence was 2.8 times higher in the HI/AA group compared with that in the non-HW group (95% confidence interval: 1.2–6.5).

CONCLUSION: Our data show that the driving forces for the discrepancy in severity of CD are older age and race/ethnicity. Importantly, the risk for persistent and recurrent CD was higher in minority children.

An estimated 1–1.5 per million children are affected by Cushing syndrome every year; of those cases, 75–80% are caused by an adrenocorticotropic hormone-secreting pituitary tumor (Cushing disease, CD) (1). Prolonged exposure to excess glucocorticoids leads to obesity, growth deceleration, striae, muscle weakness, 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 do white children; in addition, socioeconomic status (SES) is associated with poor survival in childhood leukemia (8,9). Five-year survival rates among Hispanic (HI; 74%) and African-American (AA; 75%) children remain poorer than those among non-Hispanic Whites (non-HW; 85%) for CNS malignancies as well as for many other tumors (5,10). Although 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 for other disease states when severity scores were being formulated, we looked at the co-morbidities associated with CD. Each of the individual factors used in the scoring system has independently been associated with an increased risk for a poor outcome in patients (degree of hypercortisolemia, impaired glucose tolerance, hypertension, height impairment, body mass index (BMI), delay in diagnosis, and larger tumor) (3,11,12). Our severity score aims to quantify the magnitude of glucocorticoid exposure 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 when compared with adults with CD. In adults with CD, hypertension and

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Received 2 November 2016; accepted 12 February 2017; advance online publication 17 May 2017. doi:10.1038/pr.2017.58

Table 1. Cushing disease severity score

Severity score component	To capture	Cutoff	Component score
S1	Degree of hypercortisolemia	MSC and/or 24-h UFC < 50% ile	0
		MSC and/or 24-h UFC ⩾ 50–< 75% ile	1
		MSC and/or 24-h UFC ⩾ 75% ile	2
S2	IGT	FPG < 100 mg/dl	0
		FPG ⩾ 100 mg/dl	1
		FPG ⩾ 126 mg/dl and/or DM-Dx	2
S3	Hypertension	SBP and 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 and invasion)	Adenoma size < 5 mm	0
		Adenoma size ⩾ 5 mm and/or CS invasion	1

24-h UFC, 24-h urine-free cortisol; BMI, body mass index; BP *z* score, blood pressure *z* score; CS, cavernous sinus; DBP, diastolic blood pressure; DM, diabetes mellitus; DM-Dx, diabetes mellitus diagnosis; DM-Tx, diabetes mellitus treatment with insulin or metformin at diagnosis; FPG, fasting plasma glucose; HTN-Tx, on medication for hypertension at diagnosis; IGT, impaired glucose tolerance; MSC, midnight serum cortisol; SBP, systolic blood pressure; *t* (to diagnosis), duration from first symptoms to diagnosis.
SI conversion factors: to convert fasting plasma glucose to mmol/l, multiply values by 0.0555. CD severity Score = sum of S1–S7.

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 for persistent disease and/or relapse.

METHODS

Subjects

Patients with CD ⩽ 18 years at the time of transsphenoidal surgery were consecutively treated at the National Institutes of Health Clinical Center from 1 January 1997 to 1 January 2015. Informed consent and assent was obtained from all patients. The Institutional Review Boards of the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health 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 h before the test; cortisol and adrenocorticotropic hormone levels were drawn at 2330 and 2400 hours; these values were averaged to become the 'average' late-night cortisol value. Pre-operative evaluation included (i) 24-h urinary-free cortisol, (ii) average late-night (2330 and 2400 hours) and morning (0730 and 0800 hours) serum cortisol levels, and (iii) average morning (0730 and 0800 hours) plasma adrenocorticotropic hormone levels. The initial visit data included age at surgery, gender, race/ethnicity (by self-report), number of transsphenoidal surgeries, years of hypercortisolism (as determined by a review of the 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, BMI, and BMI *z* score. BMI (kg/m^2) 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 on thr basis of a review of the most clinically relevant manifestations in children, the co-morbidities associated with CD, and the independent association of each factor with risk for 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 cutoffs 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 to 10. Estimated income data were 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 as means and SD's, unless otherwise indicated. Groups were defined on the basis of self-reported racial and ethnic descriptions, and were categorized as HI/AA if they indicated Hispanic or Latino ethnicity or indicated Black/African-American race regardless of ethnicity. The non-HW category consisted of those who indicated not being Hispanic or Latino for ethnicity and being 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 means of the χ^2 or Fisher's exact test, and the 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

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 ($n=84$)	P value[a]	Hispanic or African-American (n=45)	P value[b]
Age (years)	13.4 ± 3.5	13.8 ± 2.2	12.9 ± 3.2	0.61	13.5 ± 3.3	0.34
BMI z score	1.9 ± 0.8	2.4 ± 0.4	2.1 ± 0.7	0.25	2.0 ± 0.8	0.64
Height z score	− 1.4 ± 1.2	− 2.0 ± 1.1	− 1.1 ± 1.1	0.030*	− 1.6 ± 1.2	0.022*
Gender (F)	21 (58%)	3 (33%)	40 (48%)	0.35	24 (53%)	0.58
Median income	$29,406 ± $36,034	$66,128 ± $34,935	$59,231 ± $31,314	< 0.001[c]*	$37,466 ± $38,564	< 0.001**
Prevalence of obesity in resident state[d]				0.63		0.76
⩾ ≥ 20.1%	0	1 (11.1%)	9 (12.3%)		1 (4.6%)	
15.1–20%	3 (23.1%)	4 (44.4%)	22 (30.1%)		7 (31.8%)	
10.1–15%	10 (76.9%)	4 (44.4%)	37 (50.7%)		14 (63.6%)	
5.1–10%	0	0	5 (6.9%)		0	
0–5%	0	0	0		0	
Pediatric endocrinologist per-capita score[e]	3.9 ± 1.0	3.6 ± 1.5	3.3 ± 1.2	0.29	3.7 ± 1.2	0.097
Individuals from a developing country	18 (50%)	0	3 (3.6%)	< 0.001[f]*	18 (40.0%)	< 0.001**

BMI, body mass index; F, female; US, United States.
Data are mean ± SD or frequency (percent). Sums may not add up to total numbers due to being missing or not applicable (i.e., state information for non-US patients). *$P \leqslant 0.05$, **$P \leqslant 0.01$.
[a]P values: comparing all three groups
[b]P values: comparing combined Hispanic or African-American to non-Hispanic White.
[c]*Post hoc*-corrected $P = 0.011$ for Hispanic vs. African-American and $P < 0.001$ for Hispanic vs. non-Hispanic White.
[d]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%), and 5 (0–5%).
[e]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), and 5 (1:1–49,999).
[f]*Post hoc*-corrected $P = 0.013$ for Hispanic vs. African-American and $P < 0.001$ for Hispanic vs. non-Hispanic White.

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 < 0.05, or the relative risk 95% confidence interval excluded 1.0. Corrected P values are reported for *post hoc* comparisons, which utilized the Bonferroni method. Analyses were carried out using SAS v9.4 (SAS Institute, Cary, NC).

RESULTS

From an initial population of 139 pediatric CD patients admitted to the National Institutes of Health Clinical Center between the years 1997 and 2015, data were collected retrospectively from records of children diagnosed with CD at age ⩽18 years (64 girls and 65 boys; 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 the year at which standardization of racial and ethnic designations was 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 data sets, stratified by race/ethnicity showing HI, AA, and non-HW data individually as well as HI and AA grouped together, are presented in **Tables 2** and **3**.

The median income was higher in the non-HW group, and fewer participants from the non-HW group were from developing countries (both $P<0.001$; **Table 2**) compared with those in the HI/AA group. The developing countries where our patients reside, followed by the number of patients from each country, are as follows: Peru (5), Chile (4), and Brazil (3), and one child each from Colombia, Ecuador, Guatemala, Venezuela, Uruguay, and Argentina.

Midnight cortisol levels were higher in the HI/AA group (23.3 ± 22.0 vs. 16.2 ± 8.5 μg/dl, $P=0.040$), and height SD score was more severely affected (−1.6 ± 1.2 vs. − 1.1 ± 1.1, $P=0.022$), when compard with the non-HW group. Tumor size was also larger in the HI/AA group (6.3 ± 7.1 vs. 3.2 ± 3.3 mm, $P=0.007$).

The mean CD severity score of the HI/AA group was worse than that of 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 ($r_p=0.23$, $P=0.008$), whereas 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 resides in a developing country were not independent driving factors. Considering these effects together in multiple

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[a]	Hispanic or African-American ($n=45$)	P value[b]
MSC (μg/dl)	25.1 ± 23.9	16.1 ± 10.3	16.2 ± 8.5	0.038[c]*	23.3 ± 22.0	0.040*
24-h UFC (μg/24 h)	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[d]*	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[e]*	4.9 ± 2.0	0.023*

24-h UFC, 24-h urine-free cortisol; CD, Cushing disease; 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; MSC, midnight serum cortisol; t (to diagnosis), duration from presentation of symptoms to time of diagnosis
Data are mean ± SD or frequency (percent).
SI conversion factors: to convert midnight cortisol to nmol/l, multiply values by 27.588. To convert 24-h urinary-free cortisol (μg/24 h) to nmol/24 h, multiply values by 2.76 (molecular weight = 362.5). *$P \leqslant 0.05$, **$P \leqslant 0.01$.
[a]*P*-values: comparing all three groups.
[b]*P*-values: comparing combined Hispanic or African-American to non-Hispanic White.
[c]*Post hoc*-corrected $P = 0.040$ for Hispanic vs. non-Hispanic White.
[d]*Post hoc*-corrected $P = 0.041$ for Hispanic vs. non-Hispanic White.
[e]*Post hoc*-corrected $P = 0.014$ for African-American vs. non-Hispanic White.

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 five patients who did not achieve remission after surgery, two underwent radiation therapy and three were managed with ketoconazole. Long-term follow-up was available in 112 patients (87%) with mean postoperative follow-up of 45.5 ± 39.9 months, median follow-up of 27.9 months (interquartile ra = 13.2–68.7 months), and range of 1.4–158.7 months. Interestingly, a follow-up was available in more non-HW individuals, 78/84 (93%), as compared with HI/AA individuals, 34/45 (76%) ($P = 0.012$), 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 a 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 of 49.2 ± 28.2 months (range of 1.9–111.3 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 transsphenoidal surgery 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 five 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 a long-term follow-up or known persistence of disease after surgery, a higher proportion of individuals in the HI/AA group had a lack of initial cure or recurrence (10 out of 35 AA/HI individuals, 28.6%) when compared with the non-HW group (8 out of 78, 10.3%, $P = 0.024$). The relative risk for persistent CD combined with recurrence was 2.8 times higher in the HI/AA group as compared with that in the non-HW group (95% confidence interval: 1.2–6.5). When disease-free survival was compared (time in remission), the median for HI/AA individuals was 26.8 (95% confidence interval: 13.2–50.3) months, whereas that for non-HW individuals was 34.8 (95% confidence interval: 19.7–60.1) months; log-rank $P = 0.028$ (**Figure 1**).

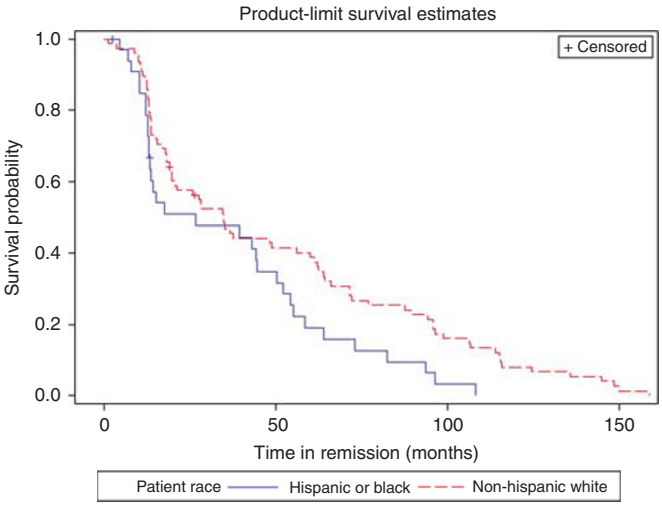

Figure 1. The Kaplan–Meier curves for disease-free survival in HI/AA and non-HW study groups (time in remission): HI/AA median = 26.8 (95% CI: 13.2–50.3) months vs. non-HW median = 34.8 (95% CI: 19.7–60.1) months; log-rank $P = 0.028$).

DISCUSSION

Our findings show disproportionately higher severity of CD in 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 with Whites (24). For all cancer sites combined, residents of poorer countries have higher death rates from cancer compared with those residing in more affluent countries (25). Later stage at diagnosis of cancer has been associated with lower SES (6). It was observed that the HI/AA children in our study had a higher rate of 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. The prevalence of obesity in non-Hispanic White youth and young adults is 14.1%, whereas the prevalence in 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 HI/AA children with CD. Transsphenoidal surgery 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 neuro-oncological care (29). In addition, minorities with cancer are under-represented 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, 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 noninvasive will enhance a long-term outcome; late pituitary CD diagnoses are associated with more co-morbidities and higher recurrence and mortality rates (3). Awareness of the signs and symptoms of CD needs to be increased among care providers. We suggest that the American Cancer Society and American Cancer Society Cancer Action Network together should influence public policies and promote patients' navigators and medical homes 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 toward 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 National Institutes of Health 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 children, and a nearly threefold higher risk for persistent CD or recurrent disease after surgery. Our data show that the driving forces for the discrepancy in disease severity are older age at the time of treatment as well as race. Delayed diagnosis and treatment and lack of access to care for these underserved children may contribute to presentation at a later age and to increased morbidity. We speculate that delayed diagnosis and treatment, barriers to access to medical care, and poorer-quality healthcare 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.

STATEMENT OF FINANCIAL SUPPORT

This research was supported in part by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health.

Disclosure: The authors declare no conflict of interest.

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