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Clinical Research Article

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Racial Disparities in Acromegaly and Cushing's Disease: A Referral Center Study in 241 Patients

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Abbreviations: ACM, acromegaly; ACTH, adrenocorticotropin; CD, Cushing's disease; GH, growth hormone; IQR, interquartile range; MHI, mean household income; SES, socioeconomic status; TSS, transsphenoidal surgery.

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Abstract

Context: Acromegaly (ACM) and Cushing's disease (CD) are caused by functioning pituitary adenomas secreting growth hormone and ACTH respectively.
Objective: To determine the impact of race on presentation and postoperative outcomes in adults with ACM and CD, which has not yet been evaluated.
Methods. This is a retrospective study of consecutive patients operated at a large-volume pituitary center. We evaluated (1) racial distribution of patients residing in the metropolitan area (Metro, N = 124) vs 2010 US census data, and(2) presentation and postoperative outcomes in Black vs White for patients from the entire catchment area (N = 241).
Results. For Metro area (32.4% Black population), Black patients represented 16.75% ACM ($P = .006$) and 29.2% CD ($P = .56$). Among the total 112 patients with ACM, presentations with headaches or incidentaloma were more common in Black patients (76.9% vs 31% White, $P = .01$). Black patients had a higher prevalence of diabetes (54% vs 16% White, $P = .005$), significantly lower insulin-like growth factor (IGF)-1 deviation from normal ($P = .03$) and borderline lower median growth hormone levels ($P = .09$). Mean tumor diameter and proportion of tumors with cavernous sinus invasion were similar. Three-month biochemical remission (46% Black, 55% White, $P = .76$) and long-term IGF-1 control by multimodality therapy (92.3% Black, 80.5% White, $P = .45$) were similar. Among the total 129 patients with CD, Black patients had more hypopituitarism (69% vs 45% White, $P = .04$) and macroadenomas (33% vs 15% White, $P = .05$). At 3 months, remission rate was borderline higher in White (92% vs 78% Black, $P = 0.08$), which was attributed to macroadenomas by logistic regression.
Conclusion. We identified disparities regarding racial distribution, and clinical and biochemical characteristics in ACM, suggesting late or missed diagnosis in Black patients. Large nationwide studies are necessary to confirm our findings.

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Key Words: acromegaly, Cushing's disease, race, racial differences, transsphenoidal surgery, remission

Growth hormone (GH) and adrenocorticotropin (ACTH)-secreting pituitary adenomas represent 10% to 20% of all pituitary adenomas [1-5]. Hormone hypersecretion leads to clinical manifestations of acromegaly (ACM) and Cushing's disease (CD). While the incidence rates are thought to be low (approximately 0.3/100 000/year for each), ACM and CD lead to comorbidities and decreased survival compared with the general population. Timely treatment and biochemical control improve survival and comorbidities [6, 7]. Primary treatment for GH- and ACTH-secreting pituitary adenomas is transsphenoidal surgery (TSS), and lower surgical morbidity and mortality were demonstrated at high- compared with low-volume centers [8-10].

According to the US Central Brain Tumor Registry, the Black or African American population aged 15-39 have a higher incidence of pituitary adenomas than the White population (3.80 vs 3.15), with a further increase after age 40 (10.47 Black vs 4.99 White) [11]. Racial distribution specifically in patients with GH- and ACTH-secreting pituitary tumors has not been studied. Also, no studies have compared the clinical characteristics, biochemical parameters, imaging, and surgical biochemical remission between the 2 racial groups.

Emory Pituitary Center is a high-volume tertiary referral facility in Atlanta, Georgia, a large city with a diverse population. The catchment area extends throughout Georgia and surrounding states. Our study aims were to (1) compare racial distribution of operated patients from MetroATL with the US census, and (2) determine differences between clinical, biochemical, and radiological presentation and compare biochemical outcomes across racial categories for patients from the entire catchment area of the center.

Material and Methods

Patients

Of the 1836 TSSs for pituitary adenomas recorded in the Emory Pituitary Center Database (REDcap 7.6.9) between 1994 and 2016, we identified all patients ages 18 or older with ACM and CD. All patients were operated on by a dedicated pituitary neurosurgeon (N.M.O.). We determined racial categories (Black or African American, American Indian or Alaska Native, Asian, White or Caucasian, Native Hawaiian or Other Pacific Islander, Other or Unknown or Unavailable or Unreported) from the electronic medical record containing self-reported data. For the purpose of this study, due to the small number of minority patients in some race categories, we included "Other" as a racial category in addition to White, Black, and Asian. We could not ascertain the Hispanic vs non-Hispanic ethnicity due to incomplete self-reporting.

Study Design

We performed a retrospective chart review to confirm the preoperative biochemical diagnosis of ACM and CD according to the most recent Endocrine Society guidelines [12, 13]. We retrieved information on demographic, clinical, biochemical, and radiological characteristics, as well as postoperative course through March 1, 2019. The study was approved by the Emory University Hospital Institutional Review Board (IRB00019648).

The study methodology had 2 parts corresponding to each study aim. Part 1 pertained only to patients residing in MetroATL, where we compared the racial distribution with the 2010 US Census Bureau data. Using Google Maps API (application programming interface), we plotted the zip codes on the MetroATL counties map. We determined the socioeconomic status (SES) based on the annual mean household income (MHI) of each county's data from the 2010 US Census Bureau data. Part 2 pertained to the entire patient population from the center's entire catchment area, where we analyzed race differences regarding clinical, biochemical, and radiological presentation, as well as long-term postoperative outcomes.

Radiological Characteristics

We defined cavernous sinus invasion as tumor extension beyond the line corresponding to the medial tangents of the 2 components of the intracavernous internal carotid artery.

Clinical Outcomes

We defined postoperative ACM remission as normal insulin-like growth factor (IGF)-1 and GH levels lower than 1 ng/mL (fasting or after an oral glucose challenge) at 3 months postoperatively, and ACM recurrence as increased IGF-1 levels during follow-up. When recurrence was suspected, additional confirmatory studies were performed, including repeated IGF-1 and GH suppression tests. For CD, remission was defined as normo- or hypocortisolism at 3 months postoperatively, and recurrence as return of hypercortisolism during follow-up. Normocortisolism was confirmed by at least 2 normal Cushing screening tests

postoperatively. Patients receiving medications to treat GH or ACTH excess at 3 months postoperatively were not considered in remission. At our center, surveillance of Cushing's disease patients no longer requiring hydrocortisone replacement consists of annual clinical evaluation and screening with late night salivary cortisol. In patients who are not good candidates for the late night salivary cortisol test (eg, shift work, smoking), low-dose dexamethasone or urinary free cortisol is used. Multiple screening tests are used in patients with clinical suspicion of recurrence and those with 1 abnormal screening test.

Adjuvant treatment with radiation and/or reoperation were recorded.

Survival status was determined with PeopleSmart (https://www.peoplesmart.com/) and confirmed with the online obituary when applicable. Cause of death was not available.

Statistical Methods

We used the 1-sample proportions test without continuity correction to determine proportional representation of racial categories compared with the census data.

We reported normally distributed variables were as mean and SD and non-normally distributed variables as median and interquartile range (IQR).

We used the T-test to compare normally distributed continuous variables among groups defined by gender and change in remission rates, respectively. We used the Kruskal–Wallis test and Wilcoxon score for non-normally distributed continuous variables, and Fisher exact test for categorical variables. We used logistic regression to determine influence of imaging (macroadenoma) and race on postoperative remission in CD.

All statistical analyses were done using SAS v9.4 statistical software. $P < .05$ defined statistical significance.

Results

Racial distribution of the total catchment area patients (112 ACM and 129 CD) is represented in Fig. 1.

Part 1: Geographical and Racial Patient Distribution

These analyses pertain only to the MetroATL population where a county-by-county comparison with the US census was feasible. Racial composition of the MetroATL population according to the 2010 US census consisted of 55.5% White, 32.4% Black, 4.8% Asian, and 7.3% other. The total MetroATL population in 2010 was 5 286 728.

Acromegaly

Sixty patients with ACM resided in MetroATL. Patient racial categories were compared with MetroATL census data: the proportions were lower for Black, higher for White, and close to expected for Asian patients (Fig. 2). There was a statistically significant difference regarding Black patients vs Black census population ($P = .006$). When we evaluated the racial distribution of patients from each county, with counties arranged from least to most populated, White patients followed the expected pattern of more patients in more populous counties, while Black patients had consistently lower than expected representation. When we arranged the counties from lowest to highest socioeconomic status, White patients were represented more broadly across SES ranges.

Cushing's disease

Sixty-five patients with CD lived in MetroATL. Patient racial distribution was grossly representative of the census data with a slight underrepresentation of the Black population (Fig. 2) which was not statistically significant ($P = .56$). Patients with CD were more evenly distributed

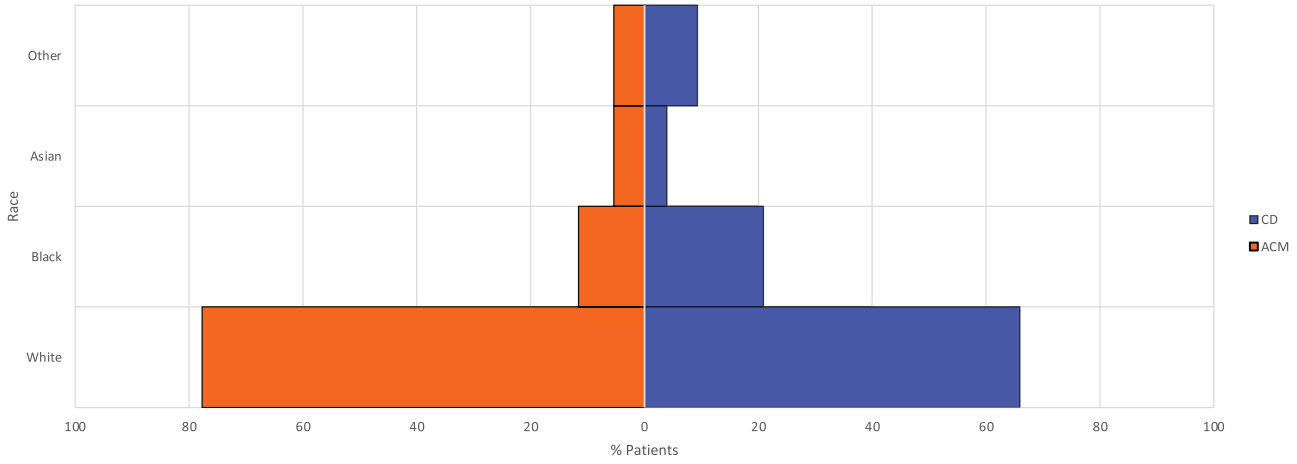

Figure 1. Racial distribution of all acromegaly (ACM, N = 112) and Cushing's disease (CD, N = 129) operated patients.

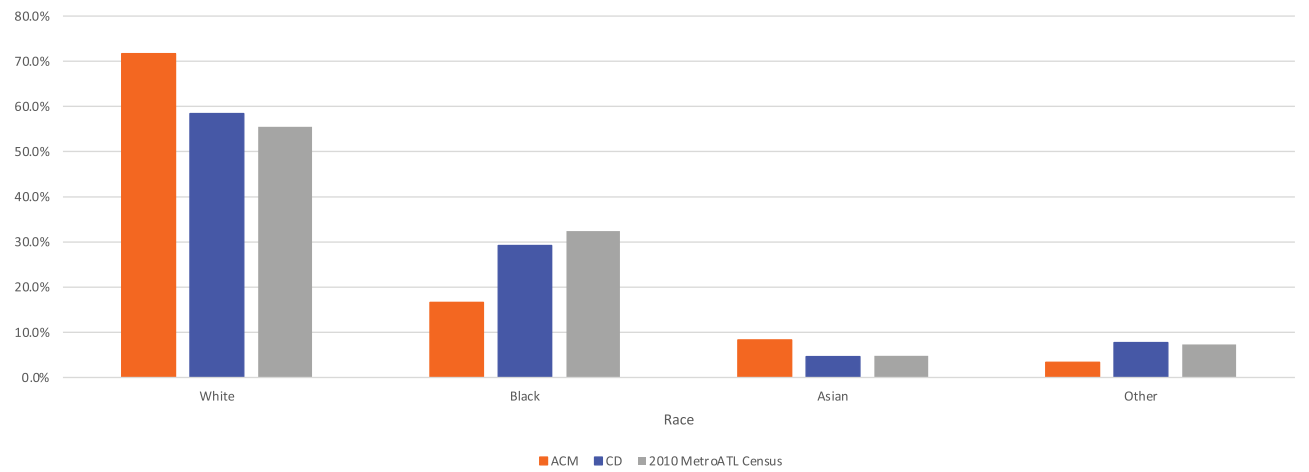

Figure 2. Racial distribution of Metropolitan Atlanta patients (60 ACM and 65 CD) and general population according to 2010 US census data.

within MetroATL counties than patients with ACM. When we evaluated the racial distribution of patients from each county, with counties arranged from least to most populated, the number of both Black and White patients was higher in the more populous counties. When we ordered the counties by mean household income, as the income increased, the number of White patients increased. We could not identify trends in Black patient representation based on the SES indicator above.

We analyzed patients' racial distribution for DeKalb County, where the tertiary referral pituitary center is located. DeKalb is 1 of the most populous counties within MetroATL (691 893 inhabitants, according to the 2010 US census) with an average annual household income that is close to the median income of the State of Georgia ($50 651). Compared with the 2010 US census (33.3% White, 54.3% Black, 5.1% Asian, and 7.3% other), ACM patient representation from this county showed racial disparities with fewer Black patients and more White and Asian than expected (62.5% White, 37.5% Black, 12.5% Asian, and 0% other). For patients with CD, the Black patient proportion was higher than expected (21.4% White, 71.4% Black, 0% Asian, and 7.1% other).

Part 2: All-patient Analyses From the Entire Center Catchment Area

Presentation and comorbidities in the Black and White racial groups

The analyses below pertain to all Black and White patients operated on for ACM and CD from both within and outside MetroATL.

In ACM, gender representation and mean age were similar for Black and White patients (Table 1). Peak age at surgery was in the sixth life decade; however, only a few Black patients were operated on after age 60 (Fig. 3). The main reason for pituitary evaluation was different across racial categories: fewer Black patients were tested because of typical physical changes (23% Black vs 44% White), while headaches/visual changes (46.1.% Black vs 17% White) and pituitary incidentalomas (30.8% Black vs 14% White) were more prevalent presentations in Black patients. Gender analyses in Black patients indicated presentation with typical physical changes in 3 women/0 men, headaches/visual changes 3 women/3 men, and pituitary incidentaloma in 2 women/2 men. Statistical differences were found when presentation with headaches or incidentaloma were considered (76.9% Black vs 31% White, $P = .01$). Black patients also had higher rates of diabetes mellitus and hypertension than White patients, with the P value in the borderline statistical range for hypertension (Table 1). Mean body mass index (BMI) was similar for Black and White patients. The proportion of patients affected by malignancies was 15% in Black and 5.7% in White patients ($P = .22$). Black patients had lower mean IGF-1 deviations from normal and borderline lower GH levels, while mean tumor diameter and proportion of tumors with cavernous sinus invasion were similar to White patients (Table 1).

In CD, peak age at surgery for Black patients was achieved in the fifth decade, followed by an abrupt decrease at older ages. White patients had a peak age in the fourth decade, followed by a more gradual decrease (Fig. 3). Black patients had higher rates of preoperative hypopituitarism than White, but similar prevalence of DM and hypertension (Table 2). The proportion of macroadenomas was higher in Black patients (33% Black vs 15% White, $P = 0.05$).

Postoperative outcomes across racial groups

Short-term (3 month) biochemical remission rates in ACM were similar in Black (46%) and White (55%) patients

Table 1. Preoperative characteristics of patients with acromegaly

Parameters	Black (13)	White (87)	*P* value
Demographic			
Age at surgery (years)	45.1 ± 13.1	46.5 ± 13.0	.75
Gender (% women)	54	53	1.00
BMI (kg/m^2)	32.4 ± 7.3	30.1 ± 6.2	.31
Comorbidities			
Hypertension (%)	69	42	.08
Diabetes mellitus (%)	54	16	.005
Hypopituitarism (%)	23	41	.24
Biochemistry			
IGF-1 (nmol/L)	86.7 ± 42.4	107.7 ± 41.9	.06
(IGF-1 – UNL)/UNL	0.9 (0.4;1.0)	1.4 (0.9; 2.6)	.03
GH (µg/L)	6.35 (4.8; 11.3)	11.2(4;38.5)	.09
Imaging			
Tumor diameter (cm)	2.1 ± 1.3	2.1 ± 1.5	.73
Cavernous sinus invasion (%)	54	39	.37

Normally distributed variables are presented as mean ± SD and non-normally distributed as median (IQR).
Abbreviations: IGF-1, insulin-like growth hormone factor 1; GH, growth hormone; UNL, upper normal limit (age and gender appropriate).

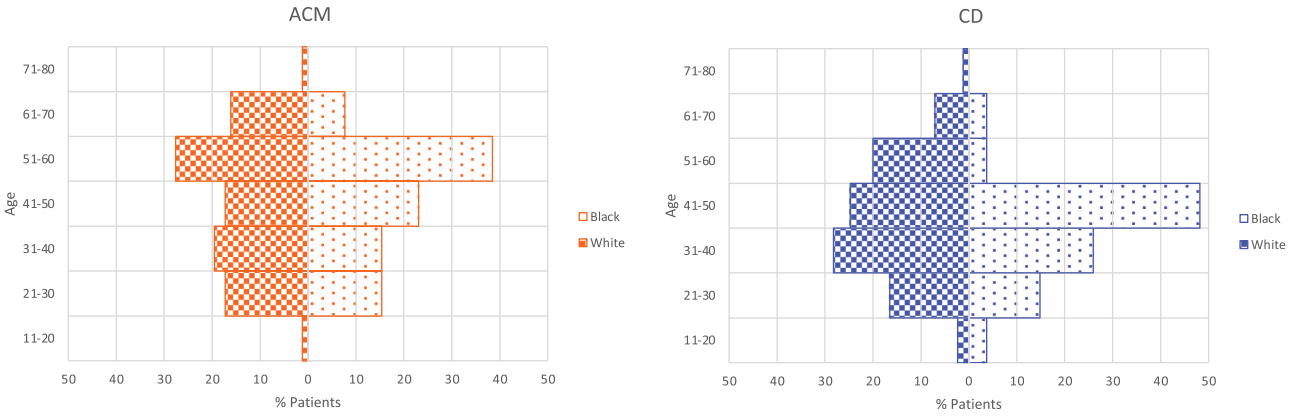

Figure 3. Racial distribution of age at surgery in ACM (N = 112) and CD (N = 129) patients. The study included patients aged 18 and older.

(*P* = .76). Long-term disease outcome parameters in ACM are presented in Table 3. There were 5 patient deaths (1 Black, 4 White) at a median of 5.9 years after surgery (IQR 3.3; 11.3). Five patients (4.4%) had biochemical recurrence (4 White, 1 undeclared race) 2.7 years after surgery (IQR 1.6; 3.8).

Short-term (3 month) and long-term disease outcome parameters in CD are presented in Table 4. Although remission rates at 3 months postoperatively were higher in White (92%) than in Black patients (78%), this was borderline significant (*P* = .08). In addition, when the statistical interaction between race, preoperative imaging, and remission was explored, the main determinant of remission was presence of a macroadenoma. There were 4 patient deaths (1 Black, 3 White) at a median of 3.3 years after surgery (IQR 2.8; 4.2). Biochemical recurrence was encountered in 1 Black and 15 White patients (*P* = .11) at a median of 2.2 years after surgery (IQR 1.0; 3.1).

Discussion

To our knowledge, this is the first study to evaluate impact of race on distribution, presentation, and outcomes of patients operated on for ACM and CD. Our main findings were underrepresentation of Black patients and milder biochemical phenotype in Black vs White patient groups in ACM. In CD, there were no major disparities regarding racial representation; however, there was a higher proportion of patients with macroadenoma and hypopituitarism and borderline lower remission rates at 3 months postoperatively in Black than in White patients.

Part 1: Racial Frequency Disparities

Primary treatment for ACM and CD is TSS. Superior outcomes were demonstrated for patients undergoing TSS at high-volume multidisciplinary centers by dedicated

Table 2. Preoperative characteristics of patients with Cushing's disease

Parameters	Black (27)	White (85)	*P* value
Demographic			
Age at surgery (years)	39.3 ± 9.5	41.9 ± 12.3	.39
Gender (% women)	74	86	.23
Body mass index (kg/m^2)	36.0 ± 9.0	35.9 ± 8.8	.98
Comorbidities			
Hypertension (%)	78	69	.59
Diabetes mellitus (%)	41	41	1.00
Hypopituitarism (%)	69	45	.04
Biochemistry			
Serum cortisol (nmol/L)	700.7 ± 386.2	681.4 ± 366.9	.77
Urinary free cortisol (nmol/day)	447.4 ± 470.3	592.6 ± 813.4	.44
Plasma adrenocorticotropin (pmol/L)	18.3 ± 13.9	17.6 ± 10.5	.81
Imaging			
Tumor diameter (cm)	1.03 ± 0.6	0.81 ± 0.55	.10
Microadenoma (%)	56	66	.08
Macroadenoma(%)	33	15	.05
No adenoma (%)	11	19	.55
Cavernous sinus invasion (%)	15	7	.25

Table 3. Postoperative course of patients with acromegaly

	Black (13)	White (87)	*P* value
At 3 months			
Biochemical remission (%)	46	55	.76
Long term			
Follow-up (years)	4.4 ± 2.7	4.4 ± 3.6	.79
Biochemical recurrence (%)	0	4.7	1.0
Reoperation (%)	0	8	.59
Radiation (%)	31	30	1.00
Last IGF-1 normal (%)	92.3	80.5	.45
Mortality	7.7	4.6	.51

Table 4. Postoperative course of patients with Cushing's disease (N = 129)

	Black (27)	White (85)	*P* value
At 3 months			
Biochemical remission (%)	78	92	.08
Long term			
Follow-up (years)	4.6 ± 3.4	4.8 ± 4.2	.93
Biochemical recurrence (%)	3.85	18.1	.11
Reoperation (%)	7.4	20	.15
Radiation (%)	18.5	16.5	.77
Mortality	3.7	3.5	1.0

neurosurgeons [9], including higher biochemical remission rates for patients with ACM [14-17] and CD [18]. Several studies indicated Black patients had the highest incidence of all types of pituitary adenomas compared with White and other racial categories [11, 19, 20]. Yet, some studies pointed out Black patients were less likely to undergo TSS for pituitary adenomas at high-volume centers [8, 10, 21, 22]. A National Inpatient Sample analysis indicated an increased number of White patients treated at centers with >25 TSS/year in recent years; however, the opposite trend was seen in minority patients [22]. The Emory Pituitary Center is the only academic high-volume pituitary center in the racially diverse region of Metro Atlanta, which offered an opportunity to evaluate the proportional representation of racial categories. Of note, our study was not designed to calculate racial prevalence of ACM and CD in the region, as it only captured patients who received treatment at our center.

We found that Black patients with ACM residing in MetroATL were less likely to undergo TSS at our center than White patients. To investigate this disparity, we evaluated factors that are known to influence patient access, such as proximity to the center and SES. We found that White patients resided in a wider geographical distribution than Black patients, and that Black patients were underrepresented even in the most populous counties. While we did not directly evaluate the patient SES and health insurance, we used the US census zip code information to account for different counties racial representation and mean household income. We noticed a wide White patient representation across SES ranges and could not identify any trends in Black patients.

For patients with CD, we did not find major disparities regarding racial distribution. Previous studies from the United States did not perform racial analyses; however, they indicate more than 80% of patients with CD undergo TSS

at large hospitals [21, 23, 24]. When we ordered the counties by mean household income, as the income increased, the number of White patients increased. This is supported by previous research showing that patients with higher SES undergo more pituitary surgeries than lower SES patients [25], and that patients with private insurance who live in wealthier neighborhoods have a higher likelihood to undergo pituitary surgery at high-volume centers [21].

Further larger studies with more medical–social correlations are needed to understand racial representation disparities we found in patients with ACM but not in patients with CD. The contrast between the higher incidence rates for all types of pituitary adenomas in Black patients (from the published studies) and our findings of underrepresentation of Black patients in ACM raises several important questions. Do SES and distance to the pituitary center play a role? While further insight can be provided by ascertaining patients' insurance status and individual income, we did not identify major frequency disparities in CD. Even more, the patient distribution in the county where the center is located (with majority Black population) confirmed that disparity occurred only in ACM. Are the features of acromegaly more difficult to recognize in Black patients? Do GH-secreting adenomas have race-specific biological characteristics?

Part 2: All-patient Analyses from the Entire Center Geographical Catchment Area

Clinical, biochemical, and radiological presentation across racial groups

We found that in patients with ACM, median IGF-1 deviation from normal was less pronounced in Black patients than White, which may result in fewer of the striking physical changes of ACM. Anthropometric characteristics play a role in recognition of the acromegaly phenotype. A survey by the National Institute for Occupational Safety and Health indicated the Black population typically had higher mean scores for 13 of the 19 facial measures than the White population, including wider faces as well as shorter, wider, and shallower noses, and that race was second to gender to impact the size and shape of the face [26]. Hence, recognition of typical facial features of ACM may be more difficult in the Black population. In our study, 68% of Black patients had imaging studies because of headaches or incidentally, while typical phenotypical changes raised suspicion for ACM in only 23%. This is an important educational point as the number of patients with serendipitously detected pituitary adenomas, including those secreting GH, has increased in recent years [27]. In the current study, Black patients with ACM had similar mean tumor size, proportion of tumors with cavernous sinus invasion, and prevalence of hypopituitarism. The lower tumoral GH secretory output may lead to less prominent physical changes, hence delays in diagnosis and an increased number of comorbidities in Black patients. Indeed, we found that more Black than White patients had diabetes at the time of surgery, along with a borderline higher prevalence of hypertension, despite similar mean BMI. Hypertension and diabetes are also more common in Black than White patients in the general population. However, the prevalence of these 2 comorbidities in our CD group was similar between Black than White patients.

In patients with CD, we found that peak age at surgery was 10 years later in Black than White patients, and that a very small number of Black patients were diagnosed after age 50. CD is suspected based on a cluster of manifestations such as centripetal weight gain, skin changes, uncontrolled diabetes, muscle weakness, or oligomenorrhea (in women), and in some patients due to acute complications such as thromboembolic disease, hypokalemia, and opportunistic infections. Our study raises the possibility of diagnostic delays in middle-aged Black women and potentially missing CD diagnosis in older Black patients. The higher likelihood of the Black general population to develop diabetes and hypertension than the White population [28, 29] may contribute to the delay. Our study also found a higher proportion of macroadenomas in Black than White patients (33% vs 15%); this would be interesting to explore in larger studies given that the majority of ACTH-secreting adenomas are small. There were no significant differences regarding mean preoperative serum or 24-hour urinary cortisol or plasma ACTH levels. Our literature search identified 1 study comparing Black with White patients which included 129 children with CD (84 White and 9 Black). In this study, both mean tumor diameter and mean urine free cortisol levels were higher in the minority group [30]. Finally, our study found hypopituitarism, but not diabetes and hypertension, to be more common in Black than White patients with CD. The etiology of hypopituitarism is multifactorial, including hypercortisolism and tumor size. Studies including a larger number of Black patients are required to elucidate this aspect.

Postoperative outcomes

Our study found similar postoperative remission rates in Black and White patients with ACM, and a long-term biochemical control of more than 80% (as a result of surgery alone or multimodality treatment with medications and/or radiation) in both racial groups. In patients operated on for CD, the short-term biochemical remission rate was higher in White patients, although this did not reach statistical significance. Of note, there was a higher proportion of pituitary macroadenomas in Black patients, which was

a stronger predictor of remission than race in the logistic regression. Presence of a macro- rather than microadenoma on magnetic resonance imaging was associated with lower remission rates than those with microadenomas in previous studies [31-33]. To date, only 1 study in children with CD evaluated surgical remission rates across racial groups and indicated a higher risk of persistent or recurrent hypercortisolism after 2.3 years (median follow-up) in the Black and Hispanic group compared with non-Hispanic White [30]. A Nationwide Inpatient Sample of 5527 adults with CD indicated mortality and postoperative endocrine and nonendocrine complications were not impacted by race; however, biochemical remission rates were not reported, and the proportion of minorities was small (6.5% Black) [24].

Study limitations are inherent to examination of rare diseases, including the retrospective design and small number of non-White patients. Inter-racial comparisons were done between the Black and White categories, due to the small number of patients from other racial backgrounds. Still, this is, to our knowledge, the first study evaluating the effect of race in ACM and CD. We did not study the influence of ethnicities, as many patients did not fill this information in the demographic questionnaires. State and regional registries are necessary to elucidate the epidemiology, characteristics, and treatment outcomes across minority populations. We calculated the expected patient racial distributions using the US census from 2010 while our study included patients operated between 1994 and 2016. However, the proportion of the Black population in Metro Atlanta progressively increased during the study span, and we did not identify racial disparities in CD. These aspects strengthen the racial distribution disparity found in Black patients with ACM. Finally, our SES analyses were exploratory in nature due to the small absolute number of Black patients. We used the annual MHI of each county's data from the US census. Other factors such as healthcare insurance, access to public transportation, and level of education remain to be explored.

In conclusion, this is the first report that underlines significant differences in clinical and biochemical presentation in Black vs White patients with ACM, which may contribute to Black patients' underrepresentation at our large-volume center. Targeted educational and healthcare delivery actions are needed to shorten the diagnostic delay and increase minority population access to referral centers. Future clinical studies are required to elucidate the race impact on ACM and CD, as well as disease-specific regional and national registries.

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Additional Information

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Data Availability: Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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