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ABSTRACT

BACKGROUND AND PURPOSE: Intracranial aneurysms have a reported prevalence of 1%–2% in the general population. Currently, only patients with a strong family history or autosomal dominant polycystic kidney disease are screened for intracranial aneurysms using MRA. The purpose of this study was to determine whether there are other specific patient populations at risk that should be offered screening for intracranial aneurysms.

MATERIALS AND METHODS: This is a retrospective case-control study of adult patients who underwent a screening MRA of their brain at our comprehensive stroke center from 2011 to 2020. Patients with a history of a known brain aneurysm were excluded. Data were extracted on patient demographics and medical comorbidities. Bivariate analyses were performed, followed by multivariable logistic regression, to identify factors associated with a positive MRA screen for incidental aneurysms.

RESULTS: Of 24,397 patients eligible for this study, 2084 screened positive for a possible intracranial aneurysm. On bivariate analysis, significant differences were present in the following categories: age, sex, race and ethnicity, chronic constipation, and hyperlipidemia. On logistic regression analysis, older age (+10 years: OR = 10.01; 95% CI, 10.01–10.02; $P = .001$), female sex (OR = 1.37; 95% CI, 1.24–1.51; $P = .001$), non-Hispanic Black (OR = 1.19; 95% CI, 1.02–1.40; $P = .031$), and Hispanic ethnicity (OR = 1.35; 95% CI, 1.16–1.58; $P = .001$) versus non-Hispanic White remained significant when adjusted for other factors.

CONCLUSIONS: Targeted screening for high-risk elderly women of Black or Hispanic descent will yield higher positive findings for brain aneurysms, which may mitigate the risk of rupture. Whether this is a cost-effective approach has yet to be determined.

ABBREVIATIONS: ADPCKD = autosomal dominant polycystic kidney disease; ICD = International Classification of Diseases

Intracranial aneurysms have a prevalence of 1%–2% in the general population.[1] Most intracranial aneurysms are saccular, a common feature in ruptured aneurysms. Intracranial aneurysms are typically diagnosed in middle-aged or elderly patients. They tend to be asymptomatic, but large aneurysms (>7 mm) may cause symptoms such as headaches, visual disturbances, and cranial nerve palsies due to mass effect.[2] In the event that an intracranial aneurysm ruptures, it causes an SAH, which has disastrous consequences; 30%–50% of patients who experience an SAH die or become permanently disabled.[3] Because most aneurysms are diagnosed as incidental findings on radiographic imaging, patients may not know that they have an intracranial aneurysm until a serious adverse event occurs. Thus, screening patients at high risk for brain aneurysm formation may offer a protective benefit.

While many studies have been conducted to identify appropriate management strategies for previously diagnosed aneurysms and risk factors predictive of rupture, few studies have addressed the question of which patient populations are at risk of having an undiagnosed intracranial aneurysm.[4,5] As per the American Heart Association guidelines, there are currently only 2 indications for which patients are offered a screening test in the form of a noninvasive MRA scan of the head.[6] Asymptomatic individuals with ≥2 affected first-degree relatives are offered this test, along with patients with autosomal dominant polycystic kidney disease (ADPCKD), due to studies that show these patient populations have a higher incidence of brain aneurysms.[7,8] However, it is imperative to understand which other factors are associated with aneurysm formation for early detection, thus allowing early intervention. To that end, as a first step, we undertook a task to build and analyze a rich 10-year data set at our institution. We defined a

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From the Departments of Neurological Surgery (K.J., S.A., D.K., G.L., A.F., R.H., D.K., N.H., D.A.) and Epidemiology & Population Health (J.Q., W.M.), Montefiore Medical Center, Bronx, New York.

Please address correspondence to David Altschul, MD, Department of Neurological Surgery, Montefiore Medical Center, 3316 Rochambeau Ave, Bronx, NY 10467-2841; e-mail: daltschu@montefiore.org; @DavidAltschulMD

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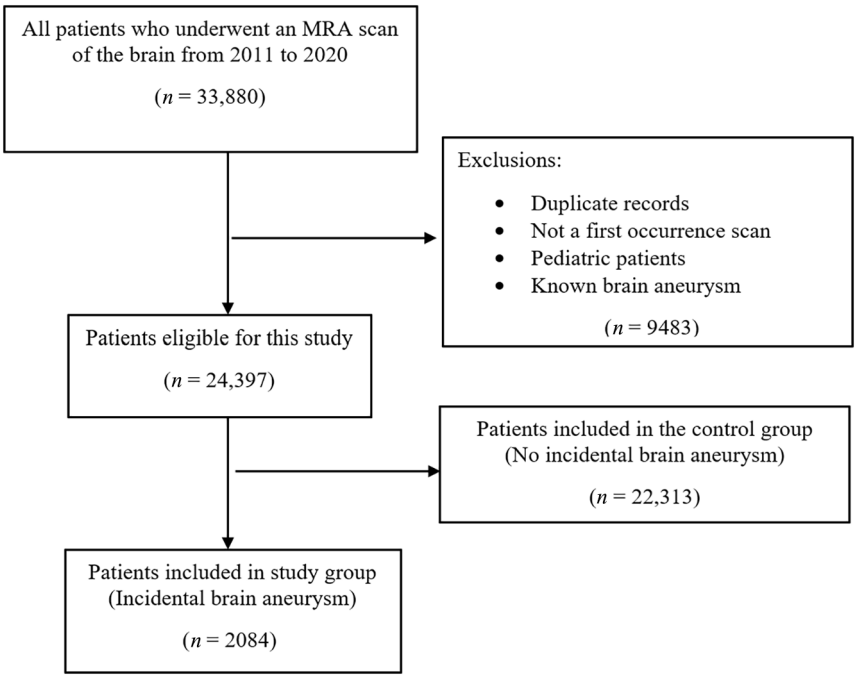

FIGURE. Flowchart depicting the cases that were included in our analysis.

sample of patients who were free of aneurysms and underwent MRA for unrelated reasons and then screened positive for a possible intracranial aneurysm. The primary objective of our study was to determine whether there were other patient populations with certain sociodemographic factors or medical comorbidities who should also be offered MRA screening for intracranial aneurysms. Our hypotheses are that patients diagnosed with long-standing hypertension, female sex, and patients with a smoking history are at increased risk for aneurysm formation because hypertension and smoking are known risk factors for aneurysm growth and rupture.[9]

MATERIALS AND METHODS

Research Ethics

Approval was obtained from the Albert Einstein College of Medicine/Montefiore Medical Center Institutional Review Board for this study (#2021–13019).

Patient Sample

This study is a retrospective cohort study. All adult patients (18 years of age and older) who underwent an MRA of the head at a single institution during a 10-year period from 2011 to 2020 were considered for potential enrollment. Patients who had a known history of an intracranial aneurysm that was being followed with routine imaging or patients who presented with an SAH due to aneurysm rupture were excluded. Only patients who were undergoing a screening MRA of the brain for an unrelated reason such as ischemic stroke, head trauma, and headache/dizziness were included. Institutional review board approval was obtained, but individual patient consent was waived, given the minimal risk posed by the study.

Data Extraction

The following steps were performed to collect data: First, a specialized software program known as mPower (Nuance; https://www.nuance.com) was used to identify all patients who underwent an MRA of the head, with or without contrast, at our hospital from 2011 to 2020. These data, including patient medical record number, date of the scan, and official MRA report, were extracted into an Excel file (Microsoft). A search was performed for duplicates, and duplicate entries were removed. If any patient had multiple MRA scans of the head, only the first index scan was included. Patients with known aneurysms undergoing surveillance MRA imaging were excluded from the study because the intention was to determine the incidence of asymptomatic unruptured brain aneurysms. All MRAs were TOF-MRA performed on either 1.5T or 3T machines. The official MRA report, which was read by an independent, blinded, experienced attending neuroradiologist at the time, was used to determine who had an incidental aneurysm. The MRA report text was searched for the following terms: focal aneurysm, small aneurysm, incidental aneurysm, large aneurysm, likely aneurysm, possible aneurysm, potential aneurysm, presumed aneurysm, probable aneurysm, segmental aneurysm, supraclinoid aneurysm, and suspected aneurysm. All cases that contained any of the aforementioned search terms were transferred to a clean file as the possible case group. All cases whose MRA report had no mention of aneurysms were kept separate as the control group.

All patients in the case group were manually reviewed by the research team. Any patient whose clinical indication for the MRA head scan was to follow-up on a known brain aneurysm was excluded. Any patient who presented with a SAH due to a ruptured aneurysm was excluded. Any patient who had an extradural aneurysm was excluded. Patients who had flow-related aneurysms associated with vascular malformations, possible mycotic aneurysms in the setting of endocarditis, and possible pseudoaneurysms after traumatic injury were excluded. Possible intracranial aneurysms of different sizes, including 1–2 mm, and different types, saccular versus fusiform, were included. If the neuroradiologist's read was unclear as to whether the observed structure was an aneurysm or an infundibulum, the case was included in the study group due to the inability to definitively rule out an intracranial aneurysm. If patients had a strong family history or known ADPCKD and were found to have an incidental aneurysm, they were included in the study group (Figure).

For patients in both the study and control groups, data were extracted on sociodemographic factors (age, sex, race and ethnicity), medical comorbidities (hypertension, hyperlipidemia, chronic constipation, and any type of renal disease including ADPCKD), and social histories (smoking history, alcohol and

cocaine use). These data were extracted from the Oracle Database called Enterprise Data Warehouse, which is affiliated with the Epic health system, using International Classification of Diseases (ICD) codes. For scans before 2016, ICD-9 codes were used, and for scans in 2016 or after, ICD-10 codes were used. In addition, for each of the previously mentioned independent variables, a number of ICD codes exist. For example, for hypertension, there are ICD codes for essential hypertension, secondary hypertension, renovascular hypertension, and so forth. All of the pertinent ICD codes for each variable were reviewed, and the presence of any of those ICD codes in the patient's chart meant that the patient had that demographic factor or medical comorbidity. For example, the variable hypertension and hyperlipidemia means that the patient was diagnosed with any type of hypertension or hyperlipidemia. Constipation refers to chronic constipation diagnosed at any time in their lives. Renal disease refers to all types of renal disease except ADPCKD, which is a separate variable. Alcohol and smoking history refer to any remote history of alcohol or cigarette use. For cocaine use specifically, patients had a history of cocaine use or had a positive urine toxicology result around the date of their MRA scan.

Statistical Analysis

Patients with incidental intracranial aneurysms in the case group were compared with patients in the control group without intracranial aneurysms on an MRA head scan. Bivariate analyses were performed to examine differences in demographic factors and medical comorbidities. Categoric variables were compared using the Pearson χ^2 test or Fisher exact test. Continuous variables were compared using Wilcoxon rank-sum tests. All variables that were evaluated on bivariate analysis were then included in the multiple logistic regression model to identify independent predictors of incidental intracranial aneurysms on screening MRA. ORs were calculated for specific racial and ethnic groups and sexes to determine which patient was at highest risk of screening positive for a brain aneurysm. All analyses were conducted using R 4.1.2 statistical and computing software (http://www.r-project.org/).[10] Statistical significance was set as $P < .05$, and all tests were 2-sided.

Table 1: Multiple logistic regression model for incidental brain aneurysm on screening MRA

Independent Predictor	OR	95% CI	*P* Value
Female sex	1.370	1.240–1.510	<.001
Age	1.010	1.010–1.020	<.001
Non-Hispanic Black	1.190	1.020–1.400	.031
Hispanic	1.350	1.160–1.580	<.001
Other race	1.180	0.980–1.410	.076
Unknown race	1.260	0.930–1.690	.134
Constipation	1.003	0.890–1.130	.956
Renal disease	1.030	0.920–1.140	.612
ADPCKD	0.930	0.370–2.340	.883
HTN	1.050	0.930–1.190	.416
Hyperlipidemia	0.970	0.870–1.080	.590
Cocaine use	1.010	0.700–1.450	.954
Alcohol use	1.070	0.820–1.390	.602

Note:—HTN indicates hypertension.

RESULTS

A total of 24,397 patients were enrolled in our study. Of them, 2084 patients were found to have an incidental brain aneurysm on MRA, while 22,313 patients did not. This means the incidence of brain aneurysms in our patient population was 0.85% per year. On bivariate analysis (Online Supplemental Data), 67.1% of patients with an incidental brain aneurysm were women compared with 60.3% of patients in the control group ($P < .001$). The mean age of patients with incidental aneurysms was 64 years compared with 60 years in the control group ($P < .001$). A larger percentage of Hispanic patients were found to have an incidental aneurysm than non-Hispanic patients (38.6% versus 35.6%, $P = .007$); 72.1% of patients with incidental aneurysms had a diagnosis of hypertension compared with 66.5% ($P < .001$); 49.9% of patients with incidental aneurysms had hyperlipidemia compared with 45.4% ($P < .001$); and 17.9% of patients had chronic constipation compared with 16.0% ($P = .023$). No statistically significant differences were observed in renal disease or ADPCKD. No statistically significant differences were found in alcohol or cocaine use, though there was a trend of difference in smoking history (22.3% versus 20.6%, $P = .076$).

On multiple logistic regression analysis (Table 1), the following variables were found to be independent predictors of incidental aneurysms on MRA: female sex (OR = 1.37; 95% CI, 1.24–1.51; $P < .001$), increasing age (+1 year: OR = 1.01; 95% CI, 1.01–1.02; $P < .001$), Hispanic ethnicity (OR = 1.35; 95% CI, 1.16–1.58; $P < .001$), and Non-Hispanic Black race (OR = 1.19; 95% CI, 1.02–1.40; $P = .031$).

In Table 2, ORs were estimated for specific groups on the basis of race and ethnicity, sex, and known risk factors. Black women had higher odds of having an incidental brain aneurysm compared with White men (OR = 1.63; 95% CI, 1.36–1.96; $P < .001$) and so did Hispanic women (OR = 1.85; 95% CI, 1.55–2.22; $P < .001$). Moreover, Black female smokers with hypertension had higher odds of incidental aneurysms than White men without vascular risk factors (OR = 1.88; 95% CI, 1.48–2.39; $P < .001$); this risk was also true for Hispanic female smokers with hypertension (OR = 2.13; 95% CI, 1.68–2.72; $P < .001$).

DISCUSSION

The incidence of screening positive for brain aneurysms in our patient population was 0.85% per year. The incidence of

Table 2: Multiple logistic regression model for incidental brain aneurysm on screening MRA, comparing specific racial and ethnic minorities, sexes, and known risk factors

Characteristic	OR	95% CI	*P* Value
Non-His Black woman vs Non-His White man	1.63	1.358–1.956	<.001
Hispanic woman vs Non-His White man	1.851	1.545–2.217	<.001
Non-His Black female smoker with HTN vs Non-His White man without smoking or HTN	1.879	1.478–2.388	<.001
Hispanic female smoker with HTN vs Non-His White man without smoking or HTN	2.134	1.675–2.717	<.001

Note:—Non-His indicates non-Hispanic; HTN, hypertension.

screening positive for brain aneurysms in Black and Hispanic female patients specifically was higher, 0.95% per year. Additionally, Black and Hispanic women had higher odds of screening positive for an incidental brain aneurysm compared with their White male counterparts, and the odds were even higher in Black or Hispanic women with hypertension or a smoking history. These numbers are slightly lower than previously reported expected rates; however, all patients with known aneurysms were excluded in this study.

Our results are consistent with what has previously been published in the literature. Intracranial aneurysms are typically diagnosed in older individuals and have long been considered a disease of aging.[11,12] Increasing age has been shown to be a risk factor for both aneurysm growth and aneurysm rupture. While age is a risk factor for aneurysm formation, increasing age is inversely proportional to the risk of rupture as life expectancy decreases. Similarly, female sex is a previously identified risk factor for multiple intracranial aneurysms.[13] The cause behind sex-based differences seen in aneurysm growth and rupture risk is not fully understood. However, a possible explanation takes into account the differences in sex hormones.[14,15] Older women are thought to be at an increased risk of aneurysms due to decreased estrogen levels after menopause, because estrogen has been linked to reduced aneurysm incidence in mouse models.

Our results suggest racial differences in intracranial aneurysm incidence. There are certain populations, such as certain Asian and European groups, that are reported to have a higher incidence of intracranial aneurysms.[16] This finding has not previously been reported for Hispanic and non-Hispanic Black populations per se. However, there are studies that report that Hispanics and non-Hispanic Black individuals present with SAH due to a ruptured aneurysm more often, while White patients have higher rates of unruptured intracranial aneurysms.[17,18] This phenomenon has always been explained by existing health disparities and barriers in access to health care. Black and Hispanic individuals are less likely to be diagnosed with unruptured intracranial aneurysms and are less likely to be monitored or electively treated, leading to a greater percentage of these patients presenting with a ruptured, aneurysmal SAH. However, our results suggest that perhaps these patient populations have a higher incidence of intracranial aneurysm formation as well. This increased incidence might explain why there has been an observation of increased likelihood to present with rupture.

Two established risk factors for aneurysm growth and rupture are hypertension and smoking history. Our hypothesis was that there would be a higher rate of incidental brain aneurysms in patients with these risk factors. However, they were not found to be independent predictors of incidental brain aneurysms in our study. Given the large body of evidence, our results do not negate them as important risk factors for aneurysm formation, growth, and rupture; rather, there is likely a reason why they did not reach statistical significance in our analysis. Perhaps it is because our data are not granular enough. For example, in regard to our hypertension variable, patients who were diagnosed with any type of hypertension, including newly diagnosed essential hypertension, long-standing chronic hypertension, acute hypertensive emergency, and secondary renovascular hypertension, were included. However, while some studies have shown that a diagnosis of hypertension is associated with an increased risk of aneurysm destabilization and rupture,[19] other studies have specifically identified acute changes in blood pressure, such as those seen during hypertensive emergency and preeclampsia, as risk factors for rupture.[20]

It is possible that acute changes in blood pressure lead to aneurysm formation as well. Moreover, in a study by Sundström et al[21] that aimed to evaluate risk factors for aneurysm rupture, patients' blood pressure readings were obtained at the time of enrollment. Patients who had persistently elevated blood pressure, suggesting that their hypertension was untreated or not adequately controlled on their current treatment regimen, were found to be at increased risk for SAH, suggesting that persistently elevated blood pressure or untreated chronic hypertension may play a greater role in contributing to aneurysm development and rupture. The role of secondary hypertension in aneurysm pathology is still being explored.[22] Our data set in its current form does not make these distinctions; thus, hypertension reached statistical significance on unadjusted analysis only. Similarly, smoking history is a well-documented risk factor for aneurysm growth and rupture due to its ability to cause vascular endothelium dysfunction and incite an inflammatory response. However, current smokers, as opposed to patients with any smoking history, have higher rates of intracranial aneurysms and present with SAH in larger numbers.[21,23] However, we tested for associations between aneurysm incidence and any remote history of smoking that only reached borderline significance on bivariate analysis. This finding could suggest that smoking has a variable effect on aneurysm formation in relation to other factors such as age, hypertension, race, sex, and ethnicity.

One-time evidence-based screening is recommended for patients with ADPCKD, especially those with high-risk features such as a known family history of brain aneurysms.[24] This recommendation is because the prevalence of brain aneurysms in patients with ADPCKD is much higher than in the general population, with reports as high as 10%.[25] ADPCKD was not found to be significantly associated with incidental aneurysm findings on MRA in our analysis, likely because the number of patients with ADPCKD in our study was very small. Of 24,397 patients, only 60 patients had ADPCKD, and only 5 of them had incidental brain aneurysms. A much larger subset of patients with ADPCKD would be needed to find a statistically significant association.

Hyperlipidemia was another variable that was tested for associations with incidental aneurysms in our analysis. We defined hyperlipidemia in general terms to include both hypertriglyceridemia and hypercholesterolemia. While hyperlipidemia has been linked to abdominal aortic aneurysms, the association between hyperlipidemia and intracranial aneurysms has not been well-studied.[26] Our results suggest that any association between hyperlipidemia and intracranial aneurysms is likely confounded by race, age, or another variable.

Last, chronic constipation was another variable that we considered for possible association with intracranial aneurysm. It has long been theorized that patients with chronic constipation who strain to defecate may have a higher incidence of

intracranial aneurysms because straining can cause a sudden increase in pressure in the arterial wall, leading to breakdown and aneurysm formation. However, constipation was not found to be an independent predictor of incidental brain aneurysm.

One weakness of our study is that we did not assess how many patients in our case group were diagnosed with intracranial aneurysms using DSA. Another weakness is that we evaluated only variables that are known to be possible risk factors for aneurysm formation and growth as mentioned in the literature. One variable that was not assessed was a strong family history of brain aneurysms. However, this is not a variable that can be extracted from the electronic medical record as an ICD code. Additionally, there is an increased level of granularity to some of the independent variables that could be further evaluated. For example, we can investigate different types of hypertension. The ICD codes were intentionally combined into larger groups to assess overarching trends in our analysis. Last, the data-extraction process needs to be verified. All of the reports that were positive for incidental aneurysm were manually reviewed by the research team, but the control group was not due to its large sample size. However, the manual review process for the case group confirmed that our automatic search achieved an accuracy of >85%. Another potential concern is that patients who undergo MRA have a different risk of having an aneurysm than patients who do not undergo MRA. Thus, cross-sectional population studies are integral to further answer this question. However, there was no significant difference in the indication for obtaining the MRA between the aneurysm and no-aneurysm cohort. Therefore, at least in patients with symptoms that prompt vascular imaging, there appear to be specific high-risk groups with a higher likelihood of an incidental unruptured aneurysm being discovered.

CONCLUSIONS

Our study is the first of its kind to demonstrate that Hispanic ethnicity and Black race in addition to increasing age and female sex are independent predictors of incidental intracranial aneurysms. Targeted screening for high-risk elderly women of Black or Hispanic descent will likely yield higher positive findings. Currently, a strong family history and known ADPCKD are the only 2 indications for which asymptomatic individuals are screened for intracranial aneurysms. However, because these patients are historically less likely to be evaluated for unruptured intracranial aneurysms and are more likely to present with ruptured aneurysms that are associated with significant morbidity, it may be reasonable to broaden the preventative screening MRA of Black and Hispanic women after 60 years of age, especially in smokers and women with long-standing hypertension. Future analysis determining whether this approach is cost-effective is still necessary.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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