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Ethnic comparison of clinical characteristics and ischemic stroke subtypes among young adult stroke patients in Hawaii

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Abstract

Background and Purpose—Native Hawaiians and other Pacific Islanders (NHOPI) with ischemic stroke have younger age of stroke onset compared to whites. However, ethnic differences in stroke subtypes in this population have been inadequately studied.

Methods—Consecutive young adult patients (age < 55 years) who were hospitalized for ischemic stroke between 2006 and 2012 at a tertiary center in Honolulu were studied. Clinical characteristics and stroke subtypes based on pathophysiological Trial of Org 10172 (TOAST) classification of NHOPI and Asians were compared to whites.

Results—A total of 427 consecutive young adult (mean age 46.7±7.8 years) patients (NHOPI 45%, Asians 38% and whites 17%) were studied. NHOPI had a higher prevalence of hypertension, diabetes, prosthetic valve, higher body mass index, hemoglobin A1c and lower HDL compared to whites (all $P<0.05$). Stroke subtype distribution were not different between the ethnic groups. Specifically, the prevalence of small vessel disease was similar between NHOPI (26.6%), whites (28.4%) and Asians (24.8%). In the univariate analyses, the use of intravenous tissue plasminogen activator (IV tPA) was lower among NHOPI (4.7%, $P=0.01$) and Asians (3.1%, $P=0.002$) compared to whites (12.5%). In the multivariable model, NHOPI (OR: 0.35, 95% CI: 0.12–0.98) and Asians (OR: 0.23, 95% CI: 0.07–0.74) were less likely to be treated with IV tPA than whites.

Conclusion—NHOPI have greater cardiovascular risk factors than whites, but there were no differences in stroke subtypes between the ethnic groups. Furthermore, NHOPI and Asians may be less likely to be treated with IV tPA than whites.

Keywords

ethnicity; stroke in young adults; ischemic stroke

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INTRODUCTION

Minorities have been shown to have a higher burden of stroke,¹⁻³ younger age of stroke onset,³⁻⁵ worse stroke outcome,^{6, 7} and different distribution of ischemic stroke subtypes compared to whites.⁸⁻¹⁰ Specifically, higher proportion of small vessel disease (SVD)/lacunar stroke and intracranial atherosclerosis have been described among minorities.⁹⁻¹² Establishing these disparities in ischemic stroke subtypes is important in understanding the predominant stroke mechanism among the high-risk ethnic group, which may result in more focused primary and secondary stroke prevention strategy for that community.¹³ Large vessel disease may be more amenable to anti-platelet and statin therapies and revascularization procedure; fibrin-rich thrombus formation in cardioembolic stroke may be better treated with anticoagulants; and SVD from arteriosclerosis may require more intensive treatment for the underlying risk factors such as hypertension and diabetes.¹⁴ Among the young stroke population, atypical risk factors and other systemic medical conditions associated with ischemic stroke may also need to be addressed.¹⁵ Importantly, the risk of recurrent stroke after the initial stroke is different based on the ischemic stroke subtypes.¹⁶

Prior studies that compared ethnic differences in ischemic stroke subtypes have mainly focused on blacks and Hispanics. Unfortunately, Native Hawaiians and other Pacific Islanders (NHOPI) with strokes have been largely understudied since NHOPI have been historically aggregated with Asians into a single ethnic group in most prior studies. As a combined ethnic group, Asians and NHOPI may have age-specific stroke mortality that is 1.5-times higher than those of whites.¹⁷ Also, NHOPI have been reported to have a higher prevalence of major cardiovascular risk factors¹⁸ and die at a younger age from cardiovascular diseases compared to other racial-ethnic groups in Hawaii.¹⁹ Compared to the general US population, NHOPI have also been reported to have lower levels of physical activity and higher prevalence of obesity and cardiometabolic conditions.¹⁸ A recent study demonstrated that NHOPI with ischemic strokes are more than a decade younger, and they have a higher burden of cardiovascular risk factors compared to whites. Despite the overwhelming evidence of cardiovascular health disparities among NHOPI, the ethnic differences in ischemic stroke subtype in this population have not been assessed. We therefore conducted a retrospective study, exclusively on young adult stroke population in Hawaii, and compared the ischemic stroke subtypes and clinical characteristics of NHOPI and Asians with whites. We hypothesized that among the young adult stroke population, NHOPI have a higher proportion of SVD from early onset of hypertension and diabetes compared to whites.

METHODS

We received approval from the Queen's Medical Center (QMC) Research and Institutional Review Committee to conduct a single-center, retrospective study of young adults (age 55 years) who were hospitalized at the QMC between 2006 and 2012 with admission diagnosis of ischemic stroke. Waiver of consent was obtained to conduct this study. QMC is a 505-bed medical center located on Oahu, the largest hospital in Hawaii and the tertiary referral center for the Pacific Basin (Hawaii, American Samoa, the Commonwealth of the Northern

Mariana Islands, Micronesia and the U.S. territories of Guam). During the study period, QMC was the only Joint Commission-certified Primary Stroke Center for the state of Hawaii. Currently, approximately 500 cases of ischemic stroke are admitted to QMC per year, with an ethnic distribution that is representative of the general population in Hawaii.

All adult patients who were age \geq 55 years and were hospitalized at QMC between January 1, 2006 and August 31, 2012 with a diagnosis of ischemic stroke were identified using the institutional stroke database. To capture all ischemic stroke patients hospitalized at QMC, a dedicated stroke database coordinator screens the entire hospital census on a daily basis with medical record review of appropriate cases. Patients with admission diagnosis of ischemic stroke is confirmed by imaging study reports or by clinical documentation confirming the neurological deficits that are consistent with the diagnosis of stroke. Patients with admission diagnosis of other neurological symptoms (i.e., “altered mental status”, “dizziness”, “generalized weakness”, etc.) are also carefully reviewed to ensure that no stroke cases are missed. The stroke database coordinator also gets notified for any in-hospital “stroke code.” Furthermore, majority of stroke patients are admitted to a dedicated “stroke/neuro” floor or transferred to this floor when the stroke is later discovered, which increases the yield of screening process. All ischemic strokes presenting during this period were included. Patients who had ischemic stroke from procedural or surgical complication were excluded.

Baseline characteristics

Baseline demographic and clinical characteristics, including known risk factors and administration of intravenous tissue plasminogen activator (IV tPA), were obtained from a manual chart review process. The ethnicity information was collected from the hospital’s administrative database, and were obtained during the registration or admission process according to a standard institutional protocol. Because of the low number of blacks and American Indian/Alaska natives, these ethnic groups were combined with the “other” group. For this study, ethnicity was categorized as NHOPI, Asian, white or “other.” Since mixed ethnic background is relatively common in Hawaii, ethnicity was defined as the ethnic background that the patient most closely associated with and was based on patient self-identification or family’s identification if the patient was incapacitated. Additional data on body mass index (BMI), hemoglobin A1c, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were also collected if they were available. Newly diagnosed atrial fibrillation was defined as newly detected atrial fibrillation on telemetry monitoring or electrocardiogram with absence of clinical history prior to hospitalization. Newly diagnosed atrial fibrillation was not included in the descriptive summary of known risk factors.

Outcome measures

Ischemic stroke subtype was the clinical outcome measure for this study. One investigator (K.N.) subtyped all patients using clinical data that had been collected, with additional review of all original neuroimaging including brain computed tomography (CT), magnetic resonance imaging (MRI), CT or MR angiography and cerebral angiogram, and original notes when necessary. Subtyping was not fully blinded to ethnicity because names were apparent on the neuroimaging reviewing system. The pathophysiological Trial of Org 10172

(TOAST) subtyping classification was used.²⁰ SVD was defined as a clinical lacunar syndrome with classic lesion on MRI or CT. Large vessel disease was defined as carotid, vertebral, or major intracranial artery stenosis >50% in the arterial territory of the stroke. Cardioembolic stroke was based on the presence of a potential source of cardiac embolism (i.e., atrial fibrillation/flutter, intra-cardiac thrombus, prosthetic valves, or patent foramen ovale with right-to-left shunt with no other etiology to account for). All other known causes of stroke such as bacterial endocarditis, cerebral vasculitis, carotid and vertebral artery dissection, and other rare causes of stroke were designated as “other.” When no cause of stroke was found, patients were assigned to an “unknown” category. If the neuroimaging had findings that were highly suggestive of embolic stroke etiology, but there were no other data supporting the cardioembolic source, it was assigned as “unknown.”

Statistical Analysis

Data were analyzed using commercially available statistical software (SPSS 23.0, Chicago, IL). We excluded patients identified as “other” ethnicity. For primary analyses, NHOPI were compared to whites, and for secondary analyses, Asians were compared to whites. Patient characteristics and ischemic stroke subtypes of the two groups were compared using the chi-square test for categorical data, and 2-tailed t-test for normally distributed continuous variables. Multivariable analyses using a logistic regression model were performed to calculate odds ratio (OR) and 95% confidence interval (CI). Age, sex, primary language (non-English vs. English), hypertension, diabetes, hypercholesterolemia, atrial fibrillation/flutter, and smoking were included in the models. Since the univariate analysis showed ethnic differences in the treatment rate of IV tPA, similar multivariable analyses were performed to assess the impact of ethnicity on IV tPA treatment rate. Prior to initiating the study, a sample size calculation was performed, which determined that 448 patients (estimating 179 NHOPI and 80 whites) were needed to detect a 15% difference in the prevalence of SVD between NHOPI and whites with a power of 0.80 and two-sided alpha of 0.05.

RESULTS

Between January 2006 and December 2012, a total of 451 consecutive young adult patients hospitalized for ischemic stroke were identified. Twenty-four patients with ‘other’ ethnicity and 2 patients with missing ethnicity data were excluded, resulting in a total of 427 patients (NHOPI 45%, Asians 38%, and whites 17%) that were included in the analyses. Unadjusted analyses (Table 1) showed that NHOPI were more likely to be female, married, non-English speaking, and were more likely to have hypertension, diabetes, prosthetic valve, higher LDL, lower HDL, higher BMI and hemoglobin A1c than whites. NHOPI were also less likely to receive IV tPA treatment than whites. Asians were more likely to be non-English speaking and have higher total cholesterol and LDL, and were also less likely to receive IV tPA treatment than whites.

Differences in stroke subtype between the NHOPI and whites, and Asians and whites are shown in Table 2. The prevalence of stroke due to SVD/lacunar were similar between the NHOPI (26.6%), Asians (24.8%) and whites (28.4%) ($P = NS$) both in unadjusted analyses

and also after controlling for age, sex, primary language, hypertension, diabetes, hypercholesterolemia, atrial fibrillation/flutter, and smoking. There was a trend toward lower prevalence of cardioembolic etiology among Asians compared to whites (OR: 0.49; 95% CI: 0.24 – 1.02, $P=0.06$). Newly diagnosed atrial fibrillation was observed similarly among the ethnic groups with 1 (1.4%) whites, 7 (4.3%) Asians, and 7 (3.6%) NHOPI ($P=0.51$ for group comparison).

The IV tPA treatment rate was significantly lower among NHOPI (4.7%, $P=0.01$) and Asians (3.1%, $P=0.002$) compared to whites (12.5%) in the univariate analyses. NHOPI and Asian ethnicity were independently associated with less likely to receive IV tPA compared to whites after adjusting for age (NHOPI, OR: 0.31, 95% CI: 0.12 – 0.79; Asians, OR: 0.20, 95% CI: 0.07 – 0.61) and in the full model (NHOPI, OR: 0.35, 95% CI: 0.12 – 0.98; Asians, OR: 0.23, 95% CI: 0.07 – 0.74) (Table 3).

DISCUSSION

In this study of young adult patients with ischemic strokes, NHOPI represented 45% of the patient population, which is substantially higher than the NHOPI representation in the community (26%),²¹ and supports the idea that NHOPI have a relatively younger age of onset for ischemic stroke. Contrary to our initial hypothesis, this study demonstrates that the distributions of ischemic stroke subtypes among the young adult population in Hawaii are similar between NHOPI, Asians and whites. Since NHOPI have a higher burden of hypertension, diabetes, hyperlipidemia and obesity even at younger age compared to whites and Asians as shown in this study, we had initially expected the NHOPI to have a higher prevalence of SVD-related strokes compared to whites and Asians; and whites and Asians with less cardiovascular risk factors to have a higher proportion of atypical causes of stroke (i.e., carotid or vertebral artery dissection, cerebral vasculitis, hematological disorder, etc.). This was based on the prior studies that suggested a higher proportion of SVD, intracranial atherosclerosis and hypertension in blacks compared to whites, possibly due to their high burden of hypertensive disease.^{9, 11, 22-25} Even though our study demonstrated a similar finding of high burden of hypertension among NHOPI, similar to the blacks in other studies, the prevalence of SVD was not much higher compared to whites. Rather, NHOPI appear to have an earlier onset of ischemic stroke without any predilection for a specific ischemic stroke subtype.

The findings from our study is important in that it may shift the conceptual framework of how we understand the etiologies of stroke disparities among NHOPI. Anecdotally, many clinicians practice with the assumption that much of the early ischemic strokes among NHOPI may be driven by SVD/lacunar strokes from uncontrolled hypertension and diabetes. However, given our study findings, we may need to further emphasize the importance of searching for other stroke etiologies including large vessel disease, cardioembolism, and other atypical causes of ischemic stroke in this ethnic group. In fact, racial/ethnic differences in the care for patients with atrial fibrillation have been reported.²⁶ Perhaps, similar disparities for the anticoagulation management for atrial fibrillation and valvular disease may also exist among NHOPI, whom had 26% cardioembolic strokes. This study also emphasizes the concept that disparities patterns may not always be the same across all

minority groups; and highlights the importance of exploring for the possibility of unexpected clinical characteristics that may exist in an understudied, multiethnic community.

Moreover, our study suggests the possibility of disparities in IV tPA treatment rate among the young adults in Hawaii. Potential factors that may explain the lower rates of IV tPA treatment among NHOPI and Asians include differences in the (1) public awareness of stroke signs and symptoms which may delay the arrival to the Emergency Department (ED), (2) modes of transportation to the ED, (3) geographic distance from the stroke center, (4) language barrier that could result in inappropriate triage by the ED staff or inaccurate assessment of the time last-seen-well, (5) proportion of ‘minor’ strokes, and (6) use of oral anticoagulants. Unfortunately, our study was not designed to assess these potential confounding factors, and thus our results on IV tPA differences should be interpreted with caution. Further study is needed to determine the contributing factors for our preliminary observation.

Strengths of our study include the detailed clinical and radiographic assessment of ischemic stroke subtypes among the multiethnic young adult population in Hawaii, which has not been done previously. However, there are some limitations to the study. More recent studies suggest that disparities in cardiovascular risk factors are primarily related to socioeconomic status (SES), and less to race/ethnicity.²⁷ Unfortunately, the data on SES were not available in our study, and thus we were unable to assess its impact on the observed disparities. Also, pre-hospital medication adherence could not be assessed from our retrospective study, which may have impacted our results. Furthermore, stroke severity measures such NIH Stroke Scale were not documented in most of our patients and could not be included in the final model. Due to the single-center study design, our results may not be generalizable to other populations. Overall, our institution captures approximately 21% of all ischemic stroke hospitalization for the state of Hawaii (data from Hawaii Health Information Corporation). Because our institution is a tertiary referral center, there may have been a referral bias toward more severe stroke patients with more extensive co-morbidities or atypical causes of stroke. Although we acknowledge the limitation of a single-center study, we believe this is an important first glance of stroke subtype distributions among the young adult ischemic stroke patients in Hawaii.

CONCLUSIONS

In a retrospective study of young adult stroke population in Hawaii, we found no ethnic differences in ischemic stroke subtypes between NHOPI, Asians and whites. Specifically, we found no relative excess of SVD among NHOPI compared to whites. Among young adults with ischemic stroke, NHOPI and Asians may be less likely to be treated with IV tPA compared to whites. However, the ethnic differences in IV tPA treatment rate is a preliminary observation and further study is needed to confirm this finding.

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Table 1
Clinical Characteristics of Young Adult (age 55) Ischemic Stroke Patients

	Whites (N = 74)	NHOPI (N = 192)	P	Asians (N = 161)	P
Age, years	48.4 ± 8.2	46.3 ± 7.9	0.06	46.4 ± 7.4	0.06
Female	18 (24.3)	84 (43.8)	0.004	55 (34.2)	0.13
Married	30 (40.5)	104 (54.2)	0.046	76 (47.2)	0.34
Non-English speaking	0 (0)	31 (16.1)	0.0003	28 (17.4)	0.0001
Hypertension	38 (51.4)	145 (75.5)	0.0001	91 (56.5)	0.46
Diabetes	17 (23.0)	89 (46.4)	0.0005	34 (21.1)	0.75
Hypercholesterolemia	20 (27.0)	71 (37.0)	0.13	38 (24.7)	0.57
Atrial fibrillation/Atrial flutter	5 (6.8)	14 (7.3)	0.88	29 (18.0)	0.51
Prior stroke or TIA	16 (21.6)	53 (27.6)	0.32	6 (3.7)	0.31
CAD or prior MI	7 (9.5)	28 (14.6)	0.27	7 (4.3)	0.12
Congestive heart failure	3 (4.1)	22 (11.5)	0.06	17 (10.6)	0.10
Peripheral vascular disease	0 (0)	4 (2.1)	0.21	2 (1.2)	0.34
Smoking	40 (54.1)	100 (52.1)	0.77	80 (49.7)	0.53
Prosthetic valve	1 (1.4)	15 (7.9)	0.046	6 (3.7)	0.32
Migraine	8 (10.8)	12 (6.3)	0.21	7 (4.3)	0.06
Methamphetamine abuse	9 (12.2)	32 (16.7)	0.36	30 (18.6)	0.22
Cocaine abuse	4 (5.4)	4 (2.1)	0.16	2 (1.2)	0.06
Total cholesterol, mg/dL *	176.4 ± 41.9	181.6 ± 51.0	0.47	199.9 ± 57.6	0.004
LDL, mg/dL *	104.0 ± 35.5	114.1 ± 43.7	0.11	124.4 ± 49.6	0.005
HDL, mg/dL *	42.0 ± 14.8	37.1 ± 11.4	0.008	43.8 ± 13.1	0.40
Triglycerides, mg/dL *	156.4 ± 136.0	165.1 ± 120.3	0.64	177.2 ± 143.4	0.33
BMI, kg/m ² *	27.8 ± 6.9	33.4 ± 8.4	<0.0001	26.6 ± 5.1	0.18
Hemoglobin A1c, % *	7.2 ± 2.5	8.9 ± 2.9	0.002	7.3 ± 2.3	0.92
IV tPA treatment	10 (12.5)	9 (4.7)	0.01	5 (3.1)	0.002

Patient characteristics. Native Hawaiians and other Pacific Islanders (NHOPI) and Asians were compared to whites (reference group). TIA, transient ischemic attack; CAD, coronary artery disease; MI, myocardial infarction; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index;

* total cholesterol, LDL, HDL and triglycerides data were available in 63 (85%) whites, 169 (88%) NHOPI and 139 (86%) Asians; BMI data were available in 64 (86%) whites, 164 (85%) NHOPI and 137 (85%) Asians; Hemoglobin A1c data were available in 38 (51%) whites, 108 (56%) NHOPI and 73 (45%) Asians. Data are n (%) or mean ± SD.

Table 2
Differences in Ischemic Stroke Subtype between NHOPI, Asians and whites

	Whites (N = 74)	NHOPI (N = 192)	Asians (N = 161)	NHOPI vs. Whites		Asians vs. Whites			
				OR	95% CI	P	OR	95% CI	P
Large vessel disease	8 (10.8)	23 (12.0)	26 (16.1)	1.11	0.42 – 2.93	0.84	1.34	0.54 – 3.33	0.53
Small vessel disease	21 (28.4)	51 (26.6)	40 (24.8)	0.63	0.30 – 1.32	0.22	0.87	0.44 – 1.71	0.68
Cardioembolic	23 (31.1)	50 (26.0)	31 (19.3)	0.88	0.43 – 1.81	0.73	0.49	0.24 – 1.02	0.06
Other stroke cause	10 (13.5)	28 (14.6)	35 (21.7)	0.92	0.36 – 2.32	0.86	1.96	0.86 – 4.48	0.11
Unknown	12 (16.2)	40 (20.8)	29 (18.0)	2.10	0.94 – 4.69	0.07	1.21	0.54 – 2.70	0.65

Ischemic stroke subtypes by ethnicity. Data are shown as n (%). Odds ratio (OR) and 95% confidence interval (CI) are shown after adjusted for age, sex, primary language, hypertension, diabetes, hypercholesterolemia (total cholesterol level >200 mg/dL), atrial fibrillation/flutter, and smoking.

Table 3
Multivariable Models for receiving IV tPA treatment

	Model 1 Unadjusted OR (95% CI)	Model 2 Adjusted for Age OR (95% CI)	Model 3 Fully Adjusted OR (95% CI)
Race			
White (reference)			-
Asian	0.21 (0.07 – 0.62) *	0.20 (0.07 – 0.61) *	0.23 (0.07 – 0.74) *
NHOPI	0.32 (0.12 – 0.81) *	0.31 (0.12 – 0.79) *	0.35 (0.12 – 0.98) *
Age		0.99 (0.94 – 1.04)	0.99 (0.94 – 1.05)
Female			0.95 (0.38 – 2.39)
Non-English as primary language			0.34 (0.04 – 2.71)
Hypertension			0.63 (0.24 – 1.67)
Diabetes			1.29 (0.47 – 3.54)
Hypercholesterolemia			1.10 (0.40 – 2.99)
Atrial fibrillation/Atrial flutter			2.49 (0.65 – 9.58)
Smoking			0.63 (0.27 – 1.48)

IV tPA, intravenous tissue plasminogen activator; OR, odds ratio; CI, confidence interval; NHOPI, Native Hawaiians and other Pacific Islanders.

* NHOPI and Asian groups were compared to whites (reference ethnic group).