Racial disparities in methamphetamine-associated intracerebral hemorrhage

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ABSTRACT

Objective: To assess racial disparities in the prevalence of methamphetamine-associated intracerebral hemorrhage (Meth-ICH) among Native Hawaiians and other Pacific Islanders (NHOPI).

Methods: Prospectively collected data from an ongoing, multiethnic, single-center cohort study were analyzed. The inclusion criteria for the cohort study required that patients be adult (age 18 years or older) residents of Hawaii with nontraumatic spontaneous intracerebral hemorrhage (ICH). Patients of race other than white, Asian, or NHOPI were excluded. Determination of Meth-ICH was made prospectively by positive urine toxicology result and lack of other clinically suspected ICH etiology. Prevalence of Meth-ICH among NHOPI was compared with that of white and Asian patients.

Results: A total of 193 patients (white 16%, Asian 61%, NHOPI 23%) were analyzed. NHOPI were younger than white (54 ± 15 vs 68 ± 15 years, respectively, $p = 0.0001$) and Asian (vs 65 ± 16 years, $p = 0.0001$) patients. Overall, 25 (13%) Meth-ICHs (mean age: 49 ± 6 years, range: 33–56 years) were identified. NHOPI had higher prevalence of Meth-ICH compared with white (24% vs 0%, respectively, $p = 0.003$) and Asian (vs 12%, $p = 0.046$) patients. The observed age differences between the racial groups persisted even after excluding the Meth-ICH group ($p < 0.01$ for all comparison).

Conclusions: NHOPI have higher prevalence of Meth-ICH compared with white and Asian patients. However, the age disparity is not entirely driven by methamphetamine abuse. *Neurology®* 2015;84:995–1001

GLOSSARY

ICH = intracerebral hemorrhage; **MAC** = methamphetamine-associated cardiomyopathy; **Meth-ICH** = methamphetamine-associated intracerebral hemorrhage; **NHOPI** = Native Hawaiians and other Pacific Islanders; **QMC** = Queen's Medical Center.

Intracerebral hemorrhage (ICH) is a severe form of hemorrhagic stroke (10%–15% of all strokes) that results in disproportionately high morbidity and mortality.[1] Minority groups, blacks and Hispanics, are the most frequently studied populations, and have been shown to have a higher incidence of ICH and younger age of disease onset than whites.[2–4] A more recent retrospective study that assessed Native Hawaiians and other Pacific Islanders (NHOPI), a racial minority group that has historically been aggregated with Asians in prior studies, also found similar disparities.[5] In that study, NHOPI with ICH were more than a decade younger than white and Asian groups, but the impact of methamphetamine, a sympathomimetic recreational drug that has been associated with ICH, was not addressed. Historically, NHOPI have a higher prevalence of methamphetamine abuse compared with other major racial-ethnic groups in Hawaii.[6–8] Therefore, it is unclear whether younger age of ICH observed in NHOPI is mostly related to the high prevalence of young methamphetamine abusers, or attributable to early onset of cardiovascular risk factors.

Therefore, we prospectively determined the prevalence of methamphetamine-associated ICH (Meth-ICH) among a population that consists of large number of NHOPI. The primary

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hypothesis was that NHOPI with ICH would have significantly higher prevalence of Meth-ICH than white or Asian population. The secondary aim was to show racial disparities after excluding the Meth-ICH group with the hypothesis that not all of the observed age differences are explained by the methamphetamine abuse in the young population.

METHODS A multiethnic prospective cohort study of patients with ICH has been conducted since July 2011 at The Queen's Medical Center (QMC) to assess racial disparities in long-term functional outcome after ICH. The clinical data that were prospectively collected for this ongoing observational cohort study were analyzed to compare the prevalence of Meth-ICH among white, Asian, and NHOPI groups. 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 US territories of Guam). QMC has the only Joint Commission–certified Primary Stroke Center and the only Neuroscience Intensive Care Unit in the state of Hawaii. Since ICH is a condition that is preferably treated in the Neuroscience Intensive Care Unit,[9] QMC is the primary referral center for acute management of patients with ICH from other major islands.

Patients. All patients with ICH hospitalized at QMC were prospectively screened for enrollment by the investigators and research staff. Inclusion criteria for the multiethnic prospective cohort study included the following: age 18 years or older; nontraumatic ICH with confirmation by CT; and resident of Hawaii for more than 3 months in a household with a telephone. Exclusion criteria were ICH related to ruptured cerebral aneurysm, ICH related to brain tumor, or hemorrhagic conversion of ischemic stroke.

Study procedures. This was an observational study and no intervention was provided. Patient demographic information (race, marital status, income level, insurance status, etc.) was obtained directly from the patients or their family if the patients were incapacitated. Since mixed racial background is relatively common in Hawaii, race was defined as the single racial/cultural background that the patient most closely associated with and was based on patient self-identification or family's identification if the patient was incapacitated. Race was ultimately categorized as white, Asian, NHOPI, or other. According to the definition used in the 2010 Census, NHOPI was defined as persons with origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.[10] Clinical and radiographic information was abstracted from the electronic medical records and was confirmed by the patients, their family, or the treating team if needed. Initial Glasgow Coma Scale score was obtained from the medical record. Regular visit to a primary care physician was defined as a minimum of one routine visit per year over the past year. All initial head CT scans were reviewed by one of the physician investigators (K.N.) using a standardized protocol. Hematoma volume was measured using the previously described ABC/2 method.[11] Presence of intraventricular hemorrhage was recorded, and ICH location was coded as deep (basal ganglia or thalamus), lobar, brainstem, cerebellum, or primary intraventricular hemorrhage.

Outcome measures. The prevalence of Meth-ICH was the clinical outcome measure for this study. Determination of Meth-ICH was made prospectively by positive urine toxicology result and lack of other clinically suspected etiology for ICH. Obtaining urine toxicology on admission for patients with ICH is a routine practice at our institution. However, the final decision to obtain this test was at the discretion of the treating physicians. Therefore, some patients with very low clinical suspicion for Meth-ICH or patients with other known causes of ICH did not have urine toxicology performed.

Standard protocol approvals, registrations, and patient consents. This study was approved by the University of Hawaii institutional review board, and written informed consent was obtained from the patient or legally authorized surrogate decision-maker.

Statistical analysis. Data were analyzed using commercially available statistical software (SPSS 22.0; SPSS, Inc., Chicago, IL). We excluded patients identified as "other" race. Patient characteristics were summarized using descriptive statistics appropriate to variable type. NHOPI were compared with white and Asian groups using the χ^2 test for categorical data, 2-tailed t test for normally distributed, continuous variables, and Mann-Whitney U test for nonparametric data (Glasgow Coma Scale). The prevalence of Meth-ICH among NHOPI was compared with that of white and Asian patients. For our secondary aim, NHOPI characteristics were compared with characteristics of white and Asian groups after excluding patients with Meth-ICH. The required sample size of 193 patients with ICH was approximated to include a minimum of 43 NHOPI and 38 white patients to detect at least 10-year age difference (SD = 16 years) between the 2 racial groups with 80% power. Levels of $p < 0.05$ were considered statistically significant.

RESULTS A total of 367 patients were screened for enrollment between July 2011 and January 2014. Of the 367 patients, the following patients were excluded: 28 patients with trauma-related ICH, 16 patients because of non-Hawaii residence, 15 patients with tumor-related ICH, 8 patients with aneurysm-related ICH, 4 patients because of ischemic stroke with hemorrhagic conversion, and one patient for age younger than 18 years. Among the remaining 295 patients, 95 patients were excluded because of no family available for consent (26), language barrier (21), expired before recruitment (12), patient/family declined (11), discharged before recruitment (9), homeless and lack telephone (6), radiographic lesion that appeared as ICH initially but was determined to be other diagnosis (5), postoperative hemorrhage (3), and prisoner (2). Seven patients of "other" race were excluded from the study: Portuguese (3), black (2), Hispanic (1), and Puerto Rican (1).

Table 1 provides the demographic and clinical information of 193 patients (white 16%, Asian 61%, NHOPI 23%) who were included in the study. Overall, NHOPI patients had younger age, lower socioeconomic status, lower rate of regular visit to their primary care physician, and higher rate of hypertension and diabetes compared with white patients. In this cohort, a total of 119 (62%) urine toxicology tests were performed. NHOPI received more frequent urine toxicology tests compared with white

Clinical characteristics of the patients with ICH by race

	NHOPI	White	Asian
No. of patients	45	30	118
Age, y	54 ± 15	68 ± 15[a]	65 ± 16[a]
Female	14 (31)	10 (33)	54 (46)
Married	24 (53)	17 (57)	65 (55)
No health insurance	8 (18)	1 (3)	12 (10)
Annual household income <$15,000	18 (40)	5 (17)[a]	20 (17)[a]
Regular visit to a primary care physician	17 (42)	21 (72)[a]	73 (67)[a]
Hypertension	37 (82)	18 (60)[a]	95 (81)
Diabetes mellitus	19 (42)	5 (17)[a]	27 (23)[a]
Hypercholesterolemia	19 (42)	15 (50)	55 (47)
Coronary artery disease	4 (9)	6 (20)	12 (10)
Atrial fibrillation	7 (16)	8 (27)	19 (16)
Coagulopathy (INR ≥1.5)	10 (22)	6 (20)	16 (14)
Methamphetamine-associated ICH	11 (24)	0 (0)[a]	14 (12)[a]
Initial SBP, mm Hg	186 ± 38	171 ± 32	175 ± 34
Initial DBP, mm Hg	105 ± 24	95 ± 22	98 ± 26
Initial GCS score	12 (4, 15)	14 (6, 15)	12 (6, 15)
Hematoma location			
Deep (basal ganglia or thalamus)	22 (49)	14 (47)	65 (55)
Lobar	12 (27)	13 (43)	36 (31)
Cerebellum	6 (13)	3 (10)	11 (9)
Brainstem	4 (9)	0 (0)	1 (1)
Primary intraventricular hemorrhage	1 (2)	0 (0)	5 (4)
Intraventricular hemorrhage	22 (49)	12 (41)	58 (50)
Hematoma volume, cm³	28 ± 32	42 ± 45	39 ± 46
Hospital length of stay, d	15 ± 19	8 ± 8	10 ± 11[a]
Do Not Resuscitate order, any	10 (33)	11 (24)	41 (35)
Hospital mortality	8 (18)	8 (27)	32 (27)

Abbreviations: DBP = diastolic blood pressure; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; INR = international normalized ratio; IQR = interquartile range; NHOPI = Native Hawaiians and other Pacific Islanders; SBP = systolic blood pressure.

[a] $p < 0.05$.

Data are n (%), mean ± SD, or median (interquartile range). NHOPI (reference group) were compared with white and Asian groups.

(80% vs 50% respectively, $p = 0.01$) and Asian (vs 58% respectively, $p = 0.01$) patients. Overall, a total of 25 (13%) patients with Meth-ICH (mean age: 49 ± 6 years; range: 33–56 years) were identified. NHOPI patients had a higher prevalence of Meth-ICH compared with white (24% vs 0% respectively, $p = 0.003$) and Asian (vs 12%, $p = 0.046$) patients.

The observed racial disparities after accounting for Meth-ICH persisted. After excluding the Meth-ICH group, NHOPI patients were still younger than white (NHOPI: 54 ± 17 years vs white: 68 ± 15 years, respectively, $p = 0.001$) and Asian (vs Asian: 67 ± 16 years, $p = 0.0001$) patients. Compared with the white and Asian groups, the NHOPI group had a higher prevalence of diabetes (NHOPI: 41% vs white: 17%, $p = 0.03$; vs Asian: 24%, $p = 0.05$) and lower rate of regular visits to their primary care physicians (NHOPI: 37% vs white 72%, $p = 0.006$; vs Asian 75%, $p < 0.0001$).

Clinical and radiographic comparisons of the Meth-ICH group (n = 25) and non–Meth-ICH group (n = 168) are shown in table 2. The Meth-ICH group had younger age, lower socioeconomic status, lower rate of regular visits to their primary care physicians, higher rate of no insurance, and presented with higher systolic and diastolic blood pressure compared with the non–Meth-ICH group. Overall, 96% of the Meth-ICHs occurred in a location that is

Table 2   Comparison of Meth-ICH and non–Meth-ICH

	Meth-ICH	Non–Meth-ICH	p Value
No. of patients	25	168	
Age, y	49 ± 6	65 ± 17	<0.0001
Female	6 (24)	72 (43)	0.07
Race			0.007
White	0 (0)	30 (18)	
Asian	14 (56)	104 (62)	
NHOPI	11 (44)	34 (20)	
No health insurance	7 (28)	14 (8)	0.003
Annual household income <$15,000	13 (52)	30 (18)	0.0001
Regular visit to a primary care physician	6 (25)	105 (68)	<0.0001
Known history of hypertension	20 (80)	130 (77)	0.77
Initial SBP, mm Hg	197 ± 33	174 ± 34	0.002
Initial DBP, mm Hg	115 ± 20	97 ± 25	0.001
Initial GCS score	11 (5, 15)	12 (7, 15)	0.89
Hematoma location			<0.0001
Deep (basal ganglia or thalamus)	15 (60)	86 (51)	
Lobar	1 (4)	60 (36)	
Cerebellum	5 (20)	15 (9)	
Brainstem	4 (16)	1 (1)	
Primary intraventricular hemorrhage	0 (0)	6 (3)	
Intraventricular hemorrhage	11 (44)	81 (49)	0.66
Hematoma volume, cm³	23 ± 27	39 ± 45	0.10
Hospital length of stay, d	9 ± 11	11 ± 13	0.54
Hospital mortality	6 (24)	42 (25)	0.91

Abbreviations: DBP = diastolic blood pressure; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; Meth-ICH = methamphetamine-associated intracerebral hemorrhage; NHOPI = Native Hawaiians and other Pacific Islanders; SBP = systolic blood pressure.
Data are n (%), mean ± SD, or median (interquartile range). Meth-ICH group was compared with non–Meth-ICH group.

considered typical for hypertensive ICH (basal ganglia, thalamus, cerebellum, or brainstem).

DISCUSSION This study showed that NHOPI have higher prevalence of Meth-ICH compared with whites and Asians, and further adds to the growing recognition of methamphetamine-related health issues in the NHOPI community.[6–8,12] Historically, methamphetamine abuse was most frequently reported in Hawaii and on the West Coast, but now has spread eastward to involve much of the United States.[13] Overall, there is an alarming increase in the general trend of substance abuse and the incidence of young strokes in the United States,[14] and highlights the importance of testing for illicit drugs and providing appropriate counseling to young patients with drug-related strokes.

Methamphetamine is a potent sympathomimetic that increases the release of dopamine, norepinephrine, epinephrine, and serotonin,[15] which result in acute hypertension and tachycardia,[16] and chronic hypertension with chronic use.[17] Methamphetamine abuse is a well-known cause of spontaneous ICH,[18–27] although the exact mechanism is unclear. Some postmortem studies have suggested acute necrotizing angiitis, leading to fibrinoid necrosis, thinning of the tunica media and intima, and microaneurysm formation.[19,27–32] However, other studies have shown no evidence of inflammation or vasculitis,[33–35] suggesting that much of Meth-ICH may be attributable to cumulative burden of methamphetamine-induced high blood pressure. In fact, 96% of Meth-ICHs in our study had hematoma in a location that is consistent with hypertensive ICH, suggesting that this may be an accelerated hypertensive pathology.

In addition to cerebrovascular toxicity, methamphetamine can cause cardiac toxicity, including cardiomyopathy, arrhythmia, coronary vasospasm, sudden

cardiac death, and dissection of aorta, coronary, and carotid arteries.[13,36] Among these conditions, methamphetamine-associated cardiomyopathy (MAC) is, perhaps, the most extensively reported cardiac pathology. Similar to Meth-ICH, the widely accepted mechanism of MAC is chronic catecholamine toxicity leading to myocardial necrosis and fibrosis, and eventually dilated cardiomyopathy.[36] Like our study, high prevalence of MAC has been reported in NHOPI among a heart failure cohort in Hawaii.[12]

In this study, even after excluding the Meth-ICH group, we were able to show that NHOPI with ICH are still significantly younger compared with white and Asian patients, which suggests that the ICH disparities are not entirely explained by the high prevalence of young methamphetamine abusers among NHOPI. Much of the observed disparities are likely attributable to early onset and higher burden of uncontrolled cardiovascular risk factors, as suggested by the lower rate of regular visits to primary care physicians by NHOPI compared with white or Asian patients.

The strength of this study is that this is the largest cohort of patients with Meth-ICH reported. Previous to our study, a retrospective study of 11 patients with Meth-ICH was the largest case series.[22] Furthermore, the diagnosis of Meth-ICH was determined prospectively in our study, which strengthens the accuracy of the diagnosis. The sample size was calculated to have enough power to detect an age difference of 10 years between NHOPI and white groups. The study site recruited a relatively large NHOPI population, which has been historically underrepresented in prior stroke studies. The limitation of this study is that this is a single-center study, which makes our results potentially not generalizable to other populations. Since the study site is located near downtown Honolulu, there may have been a geographic and selection bias toward lower socioeconomic NHOPI methamphetamine abusers who may be more likely to present to our medical center compared with other hospitals in Hawaii. However, since 81% of our cohorts were Honolulu County residents and our medical center is the primary referral center for most ICH interhospital transfers, we believe that our study population is reasonably representative of the Honolulu County. Another limitation of the study is that 21 patients were excluded because of language barrier. Since these patients are likely minorities, presumably a high proportion of other Pacific Islander population (i.e., Micronesians), exclusion of these non-English populations may have masked the impact of NHOPI race on ICH disparities. Also, it is possible that white patients with Meth-ICH were excluded from the cohort study because of lack of family consent since they may have higher likelihood of family not living in Hawaii compared with NHOPI. Furthermore, there were no ICH-free controls in this study, which weakens the argument that methamphetamine abuse was the direct cause of ICH. Lastly, we cannot exclude the possibility of selection bias toward NHOPI with Meth-ICH since urine toxicology was performed more frequently in NHOPI compared with white and Asian patients. However, many of the white and Asian patients who did not receive urine toxicology had other plausible causes of ICH, such as arteriovenous malformation or anticoagulant-related coagulopathy, making it less likely that the differences in the rate of urine toxicology performed affected our observation.

Comment:
Association or causation measures in racial disparities

Racial and ethnic disparities are well established in every subtype of stroke. An understudied group is Native Hawaiian/Pacific Islanders (NHOPI); the accompanying article by Nakagawa et al.[1] expands our knowledge about disparities involving NHOPI. Their results indicate a higher proportion of intracerebral hemorrhage (ICH) and methamphetamine-related ICH among NHOPI as compared to whites and Asians. While the numbers seem compelling, it is worth reviewing the methods and measures of association.

The study uses descriptive rather than analytic methodology. The statistical measures indicate differences in the proportion of patients with specific factors such as hypertension, diabetes, or methamphetamine exposure; while these differences suggest the presence of disparities, the lack of analytic methodology limits the conclusions substantially. To determine the greater attributable risk of methamphetamine among NHOPI vs other race/ethnic groups, a cohort followed for a period of time, during which the incidence of ICH is measured and compared by groups according to the presence or absence of any exposure of interest, in this case methamphetamine use, would be ideal. Alternatively, using a case-control methodology with cases obtained in a population-based methodology and controls matched by demographic criteria may be compared according to their exposure to methamphetamine. With either of these approaches the risk ratio or odds ratio can be estimated, strengthening the certainty of the conclusions about causal association.[2] However, at an incidence rate of 20 per 100,000 per year, a cohort of 100,000 individuals followed over 5 years would be required, making a prospective cohort study cost-prohibitive. A case-control study may require resources to obtain population-based controls and a population-wide case collection, and preliminary data such as the race/ethnic disparities reported here may support such an effort in the future.

Furthermore, it would also be ideal if the entire population were screened for the risk factor of interest. The current study included 45 total NHOPI and 30 white patients and the screening for methamphetamine use was performed in 34 (80%) NHOPI but only 15 (50%) white patients, indicating the possibility of identification/selection bias. This, in turn, affects any sample size calculation based on risk differences between groups, also limiting the conclusions. Notwithstanding these limitations, the study signals the need for further research with alternative methods to understand the determinants of ICH and the burden of typical vascular risk factors and of methamphetamine abuse in the NHOPI population.

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This study showed that Meth-ICH is not a rare cause of ICH, and is more frequently seen among young patients. NHOPI patients had a higher prevalence of Meth-ICH compared with white and Asian patients. However, even after excluding the Meth-ICH group, NHOPI still had younger age, higher prevalence of diabetes, and lower rate of regular primary care visits, suggesting that observed health disparities are not entirely driven by the methamphetamine abuse in the community.

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