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Hypertension Is A Leading Cause Of Non-Traumatic Intracerebral Hemorrhage In Young Adults

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Abstract

Objective: To evaluate the etiology and discharge outcome of non-traumatic intracerebral hemorrhage (ICH) in young adults admitted to a comprehensive stroke center.

Methods: A retrospective chart review was performed on patients with a discharge diagnosis of non-traumatic ICH admitted from 7/1/2011 to 6/30/2016. Data was collected on demographics, clinical history, ICH score, hemorrhage location, do-not-resuscitate (DNR) orders, likely etiology, and discharge disposition. Categorical data was reported as percentage. Chi-squared test was performed to evaluate association of location of ICH, etiology of ICH, and ICH score with the discharge outcome.

Results: Sixty-three patients met the study criteria, with mean age 35.4 ± 6.4 years including 26 (41%) women and 40 (64%) whites. Headache (65%) and change in mental status (48%) were the most common presenting symptoms. Hemorrhage was most commonly seen in the deep structures in 29 (46%) patients followed by lobar ICH in 14 (22%) patients. The most common etiology of ICH was hypertension in 23 (37%) patients, followed by vascular abnormalities in 18 (29%) patients. Forty-two (67%) had good outcome defined as discharge to home (n=25) or acute inpatient rehabilitation (n=17). Twenty-one (33%) patients had bad outcome with discharge to

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skilled nursing facility (n=6), hospice (n=1) or died in the hospital (n=14). Hospital DNR orders were noted in 11 (18%) patients. Higher ICH score ($p<0.0001$) and use of DNR orders ($p<0.0001$) were associated with bad outcome. All 11 patients with DNR orders died in the hospital. Location or etiology of hemorrhage were not associated with discharge outcome.

Conclusions: Hypertension, a modifiable risk factor, is a major cause of non-traumatic ICH in young adults. Aggressive management of hypertension is essential to halt the recent increased trends of ICH due to hypertension. Early DNR orders may need to be cautiously used in the hospital.

Keywords

Intracerebral hemorrhage; young adults; etiology; risk factors

INTRODUCTION:

Intracerebral hemorrhage (ICH) in the young is a devastating disease; although uncommon, it causes not only an immediate risk to life and health but leads to debility, prolonged recovery and socioeconomic hardship in prime years of productivity. ICH has been well represented in the general adult literature, but there has been a renewed interest in the young adult population due to increase in prevalence of vascular risk factors in this population.[1] ICH has been reported to comprise 3.7% to as high as 38.5% of all stroke burden in the young[2] with an incidence in one meta-analysis of 1.9 per 100,000 person-years.[3] Given the prevalence and risks of ICH, clarifying the salient characteristics of this entity in the young, with a focus on etiology is an important step in prevention and treatment. In recent studies, the rate of hypertensive ICH in patients under 45 years of age has surpassed vascular malformation as the most common contributor in young adults, especially those over 30.[4, 5] The relationship between drug abuse and ICH is also of interest, as incidence of ICH following sympathomimetic drug use has been documented as an increasingly common presentation in the young adult population.[6, 7] ICH and cocaine use have correlated with poor outcome.[8]

Although outcomes in ischemic stroke are improving, ICH when looked at across all ages has seen no change in mortality despite decline in incidence[9] and there is data lacking on outcomes and end of life decision-making in the young adult population. Compared to cerebral infarction, patients with ICH have poorer prognosis; however the prognosis of young adults with ICH are improved compared to older adult populations, suggesting age-related differences.[4]

In this study, we conducted a retrospective chart review of young adults diagnosed with non-traumatic ICH to elucidate etiologies, use of do not resuscitate (DNR) order and discharge outcomes among this population.

METHODS:

This is a retrospective study that included consecutive patients with non-traumatic ICH admitted to University of Florida Health-Shands Hospital during the 5 year period between

7/1/2011 – 6/30/2016. The study was approved by the Institutional Review Board at the University of Florida.

The study dataset of patient's aged 18 to 45 years admitted to UF Health-Shands hospital from 7/1/2011 to 6/30/2016 with ICD-9 discharge diagnosis code of intracerebral hemorrhage, 431.0 was obtained from Integrated Data Repository, Clinical and Translational Science Institute, University of Florida. The study cohort was reviewed and patients were included in this study if the age at the time of ICH diagnosis was 18–45 years, CT head was available to review and confirm ICH, and ICH was non-traumatic. Patients were excluded from the study if the age was less than 18 years or more than 45 years, had any subarachnoid hemorrhage or subdural hemorrhage, or any traumatic intracranial hemorrhage. Patients with primary intraventricular hemorrhage (IVH) were included in the study.

The charts of patients who met the above study criteria was reviewed to extract the following data points: (1) demographics, (2) medical history, (3) social history, (4) medication history, (5) presenting symptoms, (6) admission vitals including blood pressure, heart rate and body mass index, (7) use of DNR order during hospitalization, (8) complications during hospitalizations, and (9) discharge disposition. CT head images were reviewed to determine the primary location of hemorrhage: (1) lobar – frontal, temporal, parietal, occipital, (2) deep – caudate, putamen/globus pallidus, thalamus, internal capsule, corona radiata, (3) brainstem and cerebellum – midbrain, pons, medulla, and cerebellum, and (4) primary intraventricular hemorrhage. ICH score was obtained from the patient chart. ICH score was calculated from the data available in the patient's chart if it was not documented.

The etiology of hemorrhage was determined after thorough review of the chart and reported using SMASH-U etiological classification of ICH previously reported.[5, 10] It refers to structural vascular lesion (S), medication-anticoagulants (M), amyloid angiopathy (A), systemic/other disease (S), hypertension (H) and undetermined (U) etiology. Cancer was included under systemic category and amyloid angiopathy was excluded as it does not apply to patients in this study. Hypertension was determined to be the cause of hemorrhage if they had preexisting history of hypertension or diagnosed to have hypertension during hospitalization for ICH and supported by EKG or echocardiogram findings of left ventricular hypertrophy when available. Some patients underwent CT angiogram, cerebral angiogram or toxicology screen to determine the etiology of hemorrhage. Some patients had more than one etiology for ICH. The most likely single etiology was chosen for reporting the cause of ICH. Complication of ICH included the number of patients requiring intubation, temporary ventricular drainage with external ventricular drain, ventriculo-peritoeneal shunt placement, and decompression surgery. Discharge disposition included the number of patients discharged home, home with home care services, acute inpatient rehabilitation, skilled nursing or long-term care facility, hospice, or death in the hospital. Patients were considered to have good outcome if they were discharged home, home with home care services or to acute inpatient rehabilitation. Bad outcome of ICH included those discharged to skilled nursing facility, long-term care facility, hospice, or death in the hospital.

Statistical Analysis

Frequency analysis was performed to describe the patient characteristics, presenting symptoms, ICH score, primary location of hemorrhage, etiology, complications, and discharge disposition. Association of location of ICH, etiology of ICH, and ICH score with the discharge outcome was performed using Chi-squared test. Analysis was performed using SAS (Cary, North Carolina) version 9.4.

RESULTS

A total of 107 patients aged 18–45 years were admitted to UF Health-Shands Hospital between 7/1/2011 – 6/30/2016 with ICD-9 code of intracerebral hemorrhage, 431. On review of this study cohort, sixty-three patients met the study criteria.

Baseline characteristics:

The mean age of the patients was 35.4 ± 6.4 years. It included 26 (41.3%) women, 40 (63.5%) whites, 21 (33.3%) African-Americans, and 6 (9.5%) Hispanics. Baseline characteristics of young adult patients with non-traumatic ICH is listed in Table 1. Hypertension was the most common medical history present in 30 (47.6%) patients. One third had history of smoking and alcohol use. Headache (65%) and change in mental status (47.6%) were the most common presenting symptoms. Table 2 describes the frequency of each presenting symptoms, DNR orders, vitals, ICH score and primary location of hemorrhage. Eleven patients had DNR orders during the hospitalization and 5 (7.9%) patients (four patients with ICH score 4 and one with ICH score 5) had these orders documented in the first 2 days of hospitalization. Eleven of the seventeen patients with ICH score 3 to 5 were made DNR during hospitalization: 4 of 8 patients with ICH score 3; 5 of 7 with ICH score 4; and 2 of 2 with ICH score 5. Most common primary location for hemorrhage was deep structures in 29 patients (46%), followed by lobar hemorrhage in 14 (22.2%), and in brainstem and cerebellum in 16 (25.4%). Four patients (6.4%) had primary intraventricular hemorrhage.

Etiology and outcome of ICH:

According to the SMASH-U classification the etiology of ICH was structural abnormalities in 18 (28.6%), medications including anticoagulants in 3 (4.8%), systemic disease in 8 (9.6%), hypertension in 23 (36.5%), and undetermined in 11 (17.5%) patients. Four patients tested postive for sympathomimetic drug use; 3 patients for cocaine that was included in the hypertension group, and one for amphetamine who also had cavernoma. Catheter cerebral angiogram was perfomed in 18 patients and vascular abnormalities on cerebral angiogram were diagnosed in 11 patients: AV malformation or fistula in 7 patients, moya-moya type vasculopathy in 3 patients, and reversible cerebral vasoconstriction syndrome in one patient. Four patients were diagnosed with AV malformation based on CT angiogram and did not have catheter cerebral angiogram. Table 3 shows the etiology, complications, and discharge disposition of patients with non-traumatic ICH in young adults. Two-third (n=42) patients had good outcome with discharge to home or home with home services (n=25) or acute inpatient rehabilitation (n=17). One-third (n=21) patients had bad outcome with discharge to skilled or long term care facility (n=6), hospice (n=1) or death (n=14).

Among 23 patients with ICH due to hypertension, 20 had hemorrhage in deep structures, 2 in cerebellum and 1 had lobar hemorrhage. The patient with lobar hemorrahge had systolic blood pressure in 240s at admission with severe left ventricular hypertrophy on echocardiogram. Toxicology and vessel imaging was negative. Hypertension was the likely etiology in this patient and undiagnosed etiology is possible. Two patients with primary IVH had moya moya vasculopathy on cerebral angiogram. One patient had bilateral occlusion of internal carorid arteries at supraclinioid segment and pseudoaneurysm of the right posterior cerebral artery that was thought to be the cause of the IVH. The second patient with IVH had known history of ischemic stroke due to moya moya vasculopathy from sickle cell disease. No arteriovenous malformation or aneurysm was noted on this patient cerebral angiogram. The remaining two patients with IVH had AV malformations noted on angiogram.

Table 4 shows the distribution of ICH between good and bad outcome by ICH location, etiology, ICH score and DNR status during hospitalization. The location of ICH was not associated with outcome (p=0.11). However, higher proporation of patients with lobar ICH had good outcome 12/14 (85.7%). The etiology of ICH was not associated with discharge outcome (p=0.49). As expected higher ICH score was associated with bad outcome (p<0.001). All eleven patients who were made DNR during the hospitalization died. Five patients with cavernoma, and 8 of the 11 patients with AV malformation had good outcome. All four patients with primary IVH, 12 of 14 patients with lobar ICH, and 4 of 5 patients with brainstem hemorrhage had good outcome. One lobar hemorrhage due to endocarditis had bad outcome and the lobar hemorrhage due to venous sinus thrombosis had good outcome.

DISCUSSION

In this study, hypertension, a major modifiable risk factor of many disease states, was a leading cause of ICH in young adults. The frequency of hypertension as a cause of ICH is likely increasing particularly among western population and in some studies comparable to or more than that caused by vascular malformation.[5] In our study, 36.5% had ICH due to hypertension. Previous studies in western population have reported hypertension as the etiology of ICH from 11% among those aged 15–40 years in a study published in 1999[11] to 26.8% among adults aged 18–50 years in 2014[12]. In comparison to Asian studies, 46.7% of 296 adults aged 15–45 years from Taiwan, and 79.2% of 404 adults aged 16–50 years from India had hypertension as an etiology of ICH.[13, 14] Hypertension as a cause of ICH increases with age within the young adult age spectrum.[12, 14, 15] For example, in a study from Finland, 3% (2/62), 21% (14/67) and 33% (68/207) of patients aged 16–29 years, 30–39 years and 40–49 years, respectively, were diagnosed with hypertension as etiology of ICH.[14, 15]

Most of the patients in our study had a modifiable cause of their ICH – namely hypertension and sympathomimetic drug use. Notably, though not statistically significant, higher number of patients with hypertensive etiology had bad outcomes. In addition, among all patients with a bad outcome, 61.9% had ICH in deep structures of the brain, which is an area highly, correlated with hypertensive etiology. Aggressive blood pressure management in young adults with hypertension could have major impact in this regard to prevent ICH. This is

especially important because although ICH has decreased in incidence by 31% amongst all age groups, there has been no appreciable change in mortality rates between 2000 and 2010.[9] In-hospital mortality in our study was 22%. Other studies have reported rates ranging from 12.5% to 34.1% with the higher frequency reported from studies in Asia where hypertension is the most common etiology.[5, 7, 11, 13, 16]

Vascular malformations are a major non-modifiable risk factor for non-traumatic ICH in young adults. Previous studies have reported higher rates of ICH due to vascular malformations, for example 49% in the study by Ruiz-Sandoval et al,[11] and 39% by Toffol et al.[7] In our study, structural malformations accounted for 28.9% of the ICH, a decrease interpreted as a byproduct of increasing prevalence of hypertensive bleeds and possibly not earlier treatment or recognition of these entities. Considering the high incidence of vascular malformations as a cause of non-traumatic ICH and possibilities of poor outcomes in event of failure to diagnose these vascular malformations, vessel imaging should be part of all non-traumatic ICH in young adults. Diagnostic yield of vessel imaging is higher among patients younger than 50 years with lobar hemorrhage, and without history of hypertension or coagulopathy.[17, 18] Comprehensive workup is essential to prevent future risk of recurrent ICH. One study that had 78 patients with ICH reported 5-year cumulative incidence of recurrent ICH of 8.4% and all 6 patients with recurrent ICH had a vascular malformation, five AVM and one cavernoma.[12]

In terms of end-of-life care, 17.4% of patients were made DNR and 7.9% within the first two days of admission. All DNR patients died and had ICH scores more than 3. One study found placement of early DNR in the first 72 hours of admission was associated with higher ICH score of 3.[19] In a second study, patients placed under early DNR in the emergency department had no significant difference in mortality rates at 30 days compared to those without emergency department DNR for each ICH score point.[20] The mortality rates increased from 30 to 90 days for patients with DNR in the emergency department than those without DNR.[20] These two studies were performed on all adult patients with diagnosis of ICH. There is a growing body of evidence that DNR usage can be a self-fulfilling prophecy in patients with ICH and usage varies between institutions.[21] In our study, only 2 of the total 8 patients with ICH score of 3 had good outcome, and neither had a DNR order placed despite the traditional risk of mortality ascribed to such a presentation. We did not evaluate the 30-day mortality outcomes to correlate with the ICH score predictability in relation to the DNR status. This could be explored in future studies.

A major limitation of our study is the small sample size, which in future comparative studies can be expanded to more than one center using data repositories. Due to the retrospective nature of the study, we had information on only discharge disposition outcomes and functional scale outcomes were not available. Patient’s insurance and family support play a role in discharge disposition of the patient and could be a potential bias for outcome assessment.

Overall, this study lends support to an enlarging body of evidence that ICH in young adults is modifiable and driven in growing part by hypertension in a population in which chronically elevated blood pressures are not thought to be as prevalent. We have also found

that DNR orders are more frequently ordered for young patients with higher ICH scores (3 or more) who have higher likelihood of worse outcomes and were not ordered on a patient with lower ICH score and higher likelihood of good outcome.

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Table 1.

Baseline characteristics of young adults with non-traumatic ICH

Variable	No (%)
Total number of patients, no (%)	63 (100%)
Age in years, mean ± SD	35.4 ± 6.4
Gender, female, no (%)	26 (41.3)
Race, no (%)	
1. Whites	40 (63.5)
2. African Americans	21 (33.3)
3. Asians	2 (3.2)
Ethnicity, Hispanics no (%)	6 (9.5)
Medical history, no (%)	
1. Hypertension	30 (47.6)
2. Diabetes mellitus	9 (14.3)
3. Hypercholesterolemia	5 (7.9)
4. Coronary artery disease	3 (4.8)
5. Atrial fibrillation	1 (1.6)
6. Cancer (brain, colorectal, skin)	5 (7.9)
7. Sickle cell disease	3 (4.8)
Social history, no (%)	
1. Smoking	22 (34.9)
2. Alcohol use	22 (34.9)
3. Recreational drug use	14 (22.2)
a. Cocaine	6 (9.5)
b. Heroin	1 (1.6)
c. Marijuana	7 (11.1)
Medication history, no (%)	
1. Antiplatelet use	4 (6.4)
2. Anticoagulant use	3 (4.8)
3. Anti-hypertensive medication	15 (23.8)
4. Diabetic medication use	4 (6.4)

Table 2.

Clinical presentation, use of do not resuscitate order and location of non-traumatic ICH in young adults

Variable	No (%)
Presenting symptoms, no (%)	
1. Headache	41 (65.0)
2. Change in mental status	30 (47.6)
3. Weakness	21 (33.3)
4. Nausea/Vomiting	19 (30.2)
5. Change in vision	13 (20.6)
6. Sensory symptoms	10 (15.9)
7. Seizures	8 (12.7)
8. Trouble walking	6 (9.5)
9. Change in speech or language	4 (6.4)
10. Dizziness	4 (6.4)
Vitals, median (IQR)	
1. Systolic BP, mm Hg	144 (120–184)
2. Diastolic BP, mm Hg	83 (71–101)
3. Heart rate, beats/min	82 (72–95)
4. BMI	28 (23–32)
ICH Score	
1. Score 0	17 (27.0)
2. Score 1	19 (30.2)
3. Score 2	10 (15.9)
4. Score 3	8 (12.7)
5. Score 4	7 (11.1)
6. Score 5	2 (3.2)
Do not resuscitate (DNR) order, no (%)	11 (17.4)
1. DNR on day 1 or 2 hospitalization	5 (7.9)
2. DNR on day 3 or later	6 (9.5)
Primary location of hemorrhage, no (%)	
1. Lobar	14 (22.2)
2. Deep	29 (46)
3. Brainstem and cerebellum	16 (25.4)
4. Primary intraventricular hemorrhage	4 (6.4)

Table 3.

Etiology, complications, and discharge outcome of young adults with non-traumatic ICH

Variable	No (%)
Etiology	
1. Structural	18 (28.6)
a. AV malformation / AV fistula (3 lobar, 3 cerebellum, 2 deep, 2 IVH, 1 brainstem)	11 (17.5)
b. Cavernoma (2 brainstem, 1 deep, 1 cerebellum)	5 (7.9)
c. Moyo moya (2 IVH)	2 (3.2)
2. Medication - anticoagulants (2 lovenox, 1 apixaban; 2 cerebellum, 1 deep)	3 (4.8)
3. Systemic Disease	8 (12.7)
a. Cancer (3 deep, 1 cerebellum)	4 (6.3)
b. Endocarditis, cerebral venous sinus thrombosis, idiopathic thombocytopenic purpura, reversibel cerebral vasoconstriction syndrome (1 each, all lobar)	4 (6.3)
c. Sympathomimetic drug abuse (3 - cocaine, 1 -amphetamine) *	4 (6.3)
4. Hypertensive Angiopathy (20 deep, 2 cerebellum, 1 lobar)	23 (36.5)
5. Undetermined (5 lobar, 2 deep, 2 brainstem, 2 cerebellum)	11 (17.5)
Complications of ICH	
1. Required intubation	27 (42.9)
2. Ventricular drainage	
a. External ventricular drain	20 (31.8)
b. Ventriculoperitoneal shunt	7 (11.1)
3. Decompression surgery	10 (15.9)
Discharge disposition	
1. Good outcome	42 (66.7)
2. Bad outcome	21 (33.3)

* numbers included under hypertension (n=3) and cavernoma (n=1). Etiology reported using SMASH-U classification.[10]

Table 4.

Discharge outcome of non-traumatic ICH in young adults based on hemorrhage location, etiology, ICH score and use of do not resuscitate order

Variable	Good outcome, n (%) N=42	Bad outcome, n (%) N=21
Location of hemorrhage		
1. Lobar	12 (28.6)	2 (9.5)
2. Deep	16 (38.1)	13 (61.9)
3. Brainstem/ Cerebellum	10 (23.8)	6 (28.6)
4. IVH	4 (9.5)	0
Etiology of ICH		
1. Structural	15 (35.7)	3 (14.3)
2. Medication	2 (4.8)	1 (4.8)
3. Systemic	5 (11.9)	3 (14.3)
4. Hypertension	13 (31)	10 (47.6)
5. Undetermined	7 (16.7)	4 (19.1)
ICH score *		
1. Score 0	15 (35.7)	2 (9.5)
2. Score 1	16 (38.1)	3 (14.3)
3. Score 2	9 (21.4)	1 (4.8)
4. Score 3	2 (4.8)	6 (28.6)
5. Score 4	0	7 (33.3)
6. Score 5	0	2 (9.5)
DNR order use *		
1. DNR on day 1 or 2 of hospitalization	0	5 (23.8)
2. DNR on day 3 or later	0	6 (28.6)
3. No DNR	42 (100)	10 (47.6)

*Significant for $p < 0.0001$