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Clinical Study

Underlying effect of age on outcome differences in arteriovenous malformation-associated intracerebral hemorrhage

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ABSTRACT

Brain arteriovenous malformations (AVM) are the most common cause of intracerebral hemorrhage (ICH) in young adults. Although previous studies have found that the mortality and morbidity of ICH due to AVM (AVM-ICH) is lower than in spontaneous ICH, it is unclear whether the more favorable prognosis is directly related to the presence of the vascular malformation. We included 34 patients with AVM-ICH and 187 with spontaneous intracerebral hemorrhage (sICH) due to either hypertension or cerebral amyloid angiopathy. Patient data were obtained from the prospective Intracerebral Hemorrhage Outcomes Project, which enrolls ICH patients admitted to Columbia University Medical Center. Using ICH etiology (AVM-ICH or sICH) and previously verified predictors of ICH outcome, two multivariate analyses were performed with and without age to compare the odds of death at 3 months and the functional outcome. Although mortality in AVM-ICH group was lower than the sICH group (20.6% *versus* 43.3%, respectively), this value was only significant when age was excluded ($p = 0.017$) and lost its significance when we controlled for age ($p = 0.157$). There was an analogous loss of significance with functional outcome using the modified Rankin Scale. In conclusion, our data suggests that the previously observed lower case fatality rate and more favorable functional outcomes in the AVM-ICH group compared to the sICH group may largely be the result of age.

1. Introduction

Intracerebral hemorrhage (ICH) is the deadliest and second most common form of stroke, accounting for 15% of all strokes worldwide and carrying a 30–50% mortality rate [1]. Outcomes of ICH have been known to vary with clinical and radiographic characteristics such as age, Glasgow Coma Scale (GCS) score, location and size of hemorrhage, and intraventricular extension [2]. Over the past decade, however, investigators are starting to consider secondary ICH as a group of separate disease processes, which vary in their prognosis compared to primary (spontaneous) ICH and have their own predictors of outcome [3–6].

Arteriovenous malformations (AVMs), a secondary cause of ICH, is the most common etiology of ICH in younger adults [6], accounting for one-third of cases [7], and has a prevalence of roughly 18 per 100,000 adults [6]. Previous studies [8–11] have found a lower 1-month case fatality rate in ICH patients in the AVM group (AVM-ICH) compared to the spontaneous intracerebral hemorrhage group (sICH), which included patients with ICH due to hypertension and cerebral amyloid angiopathy.

More recently, a population-based series by van Beijnum et al. [4] studied two prospective databases in the United Kingdom and found that case fatality and rate of functional dependence at 2 years and 1 year follow-up were greater in the sICH group than the AVM-ICH group.

In this study, we sought to assess the prognosis of AVM-ICH in our cohort and determine whether underlying patient characteristics might explain these differences.

2. Methods

2.1. Study population

Between December 2009 and April 2014, 289 patients with spontaneous non-traumatic ICH diagnosed by admission CT scan

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were admitted to the Columbia University Medical Center Neurological Intensive Care Unit, and were prospectively enrolled in the Intracerebral Hemorrhage Outcomes Project (ICHOP). The study was approved by the Institutional Review Board, and written consent was obtained for participation in the study either from the patient or from the appropriate surrogate representative if the patient lacked capacity.

Patients were separated into two groups: ICH due to an AVM (AVM-ICH), and sICH due to hypertension, amyloid angiopathy, or idiopathic causes. AVM were diagnosed by gold-standard angiography, or if the patient was not stable enough to undergo the test, the AVM was diagnosed by MRI or CT angiography. ICH patients who also had intraventricular, subarachnoid, or subdural hemorrhage as diagnosed on CT scan were included. Similar to previous studies [4], exclusion criteria prior to our preliminary dataset of only AVM-ICH and sICH patients were ICH secondary to malignancy, trauma, hemorrhagic conversation of an ischemic stroke, or another primary bleeding event. Patients were also excluded if the hemorrhage was due to anticoagulation, coagulopathies, drugs (such as cocaine), or other vascular malformations (including cavernous malformation, venous angioma, dural arteriovenous fistula, and vein of Galen malformations). The etiology of each ICH was determined by consensus of the neurological intensive care unit team, which includes neurosurgeons, neuroradiologists, interventionalists, and neurologists. Additional exclusion criteria were patients with an international normalized ratio >1.4, platelet count <50,000/μL, patients with incomplete data, and patients <18 years old. Patients received standard care for ICH in accordance with the most up-to-date American Heart Association/American Stroke Association guidelines [12].

2.2. Clinical variables and follow-up

Demographic, radiographic, and clinical course data were prospectively collected for patients presenting with non-traumatic sICH as part of ICHOP. Clinical course data included hospital complications and length of stay. Admission CT scan, performed within 72 hours of admission, was evaluated for hematoma volume, location of the ICH, and presence of intraventricular hemorrhage (IVH). The outcomes, assessed by a follow-up telephone interview, were death at 3 months and the patient's score on the widely-used 7 point modified Rankin Scale (mRS) dichotomized into 0–3 (functional independence) and 4–6 (death or dependence).

Table 1
Basic clinical, radiographic, and hospital course characteristics in spontaneous intracerebral hemorrhage (sICH) *versus* arteriovenous malformation-intracerebral hemorrhage (AVM-ICH)

Characteristic	AVM-ICH (n = 34)	sICH (n = 187)	*p* value
Patient demographics			
Age, median (range)	43.5 (26.75–59)	66 (53–80)	<0.0001[a]
Sex, male	14 (41.2%)	102 (54.5%)	0.151[b]
Ethnicity			
White	11 (32.4%)	61 (32.6%)	0.560[b]
African–American	6 (17.6%)	53 (28.3%)	0.560[b]
Hispanic	12 (35.3%)	56 (29.9%)	0.560[b]
Asian	4 (11.8%)	12 (6.4%)	0.560[b]
ICH characteristics			
ICH score, median (range)	1.5 (1–3)	2 (1–3)	0.314[a]
Admission GCS, median (range)	13 (7–15)	10 (6–14)	0.041[a]
Infratentorial	10 (29.4%)	59 (31.6%)	0.804[b]
Supratentorial	24 (70.6%)	128 (68.4%)	0.804[b]
ICH volume, cm^3 (range)	6 (2–32.9)	15 (5–40)	0.028[a]
ICH volume $\geqslant 30$ cm^3	9 (26.5%)	62 (33.2%)	0.443[b]
Intraventricular hemorrhage	21 (61.8%)	111 (59.4%)	0.792[b]
Medical history			
Hypertension	8 (23.5%)	151 (80.7%)	<0.0001[b]
Seizures	3 (8.8%)	5 (2.7%)	0.108[b]
Diabetes mellitus type I or II	1 (2.9%)	51 (27.3%)	0.001[b]
Congestive heart failure	0 (0%)	11 (5.9%)	0.152[b]
Arrhythmias (including atrial fibrillation)	2 (5.9%)	8 (4.3%)	0.679[b]
Hyperlipidemia	4 (11.8%)	53 (28.3%)	0.042[b]
Anemias	0 (0%)	8 (4.3%)	0.612[b]
Liver disease	0 (0%)	6 (3.2%)	0.594[b]
Renal disease	0 (0%)	25 (13.4%)	0.018[b]
Cancer	0 (0%)	11 (5.9%)	0.152[b]
Dementia	0 (0%)	21 (11.2%)	0.025[b]
Total number of comorbidities			
0 or 1	33 (97.1%)	141 (75.4%)	<0.005[b]
$\geqslant 2$	1 (2.9%)	46 (24.6%)	<0.005[b]
Hospital parameters			
Length of hospitalization, days, median (range)	14 (8.5–25)	8 (4–18)	0.003[a]
Total number of hospital complications[c]			
0 or 1	15 (44.1%)	76 (40.6%)	0.705[b]
$\geqslant 2$	19 (55.9%)	111 (59.4%)	0.705[b]

Data are presented as number (%) unless otherwise stated.
[a] Mann–Whitney *U* test.
[b] Chi-squared or Fisher's exact test.
[c] Includes: fever >38.5°C, ventriculitis, myocardial infarction, pulmonary embolism, pneumonia, ventilator-associated pneumonia, urinary tract infection, sepsis, acute renal failure, hyperglycemia (serum glucose $\geqslant 200$ mg/dL), and hyponatremia (serum $Na^+ \leqslant 133$ mEq/L).
AVM = arteriovenous malformation, GCS = Glasgow Coma Scale, ICH = intracerebral hemorrhage.