SHORT REPORT

Impact of premorbid hypertension on haemorrhage severity and aneurysm rebleeding risk after subarachnoid haemorrhage

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Received 26 January 2013
Revised 24 May 2013
Accepted 31 May 2013
Published Online First 29 June 2013

ABSTRACT

Objective Arterial hypertension (HTN) is a risk factor for subarachnoid haemorrhage (SAH). We aimed to assess the impact of premorbid HTN on the severity of initial bleeding and the risk of aneurysm rebleeding after SAH.

Design Retrospective analysis of a prospective cohort study of all SAH patients admitted to Columbia University Medical Center between 1996 and 2012.

Results We enrolled 1312 consecutive patients with SAH; 643 (49%) had premorbid HTN. Patients with premorbid HTN presented more frequently as Hunt–Hess Grade IV or V (36% vs 25%, p<0.001) and World Federation of Neurosurgical Societies (WFNS) Grade 4 or 5 (42.6% vs 28.2%, p<0.001), with larger amounts of subarachnoid (Hijdra Sum Score 17 vs 14, p<0.001) and intraventricular blood (median IVH sum score 2 vs 1, p<0.001), and more often with intracerebral haemorrhage (20% vs 13%, p=0.002). In multivariate analysis, patients with premorbid HTN had a higher risk of in-hospital aneurysm rebleeding (11.8% vs 5.5%, adjusted OR 1.67, 95% CI 1.02 to 2.74, p=0.04) after adjusting for age, admission, Hunt–Hess grade, size and site of the ruptured aneurysm.

Conclusions Premorbid HTN is associated with increased severity of the initial bleeding event and represents a significant risk factor for aneurysm rebleeding. Given that aneurysm rebleeding is a potentially fatal—but preventable—complication, these findings are of clinical relevance.

INTRODUCTION

Arterial hypertension (HTN) is common and it doubles the risk of subarachnoid haemorrhage (SAH).[1] Severity of the initial bleeding event is reflected by poor clinical grade, the most important determinant of mortality and outcome after SAH. Aneurysm rebleeding is a devastating, but preventable, complication of SAH, and it is associated with additional mortality and disability.[2 3] It is unclear if premorbid HTN is associated with an increased risk of rebleeding. In this retrospective analysis of a prospectively collected database, we sought to investigate the impact of premorbid HTN on the severity of the initial bleeding event, the risk of rebleeding, clinical course, and outcome after SAH.

METHODS

We analysed all SAH patients with documented premorbid HTN status admitted to the Columbia University Medical Center Neurological Intensive Care Unit between July 1996 and April 2012 enrolled in the Columbia University SAH Outcomes Project. Consent for enrolment was obtained at the time of admission from patients or, if neurologically impaired, from family members, with institutional review board approval. Outcome was assessed at 3 months with the modified Rankin Scale (mRS).

Clinical definitions and clinical management

Premorbid HTN was defined as self-reported history of HTN or use of antihypertensive medications due to premorbid HTN or hypertensive end-organ disease (eg, hypertensive nephropathy). Antihypertensive medication was defined as: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, β-blockers. Clinical grade was assessed directly upon admission to the Columbia University Medical Center with the Hunt & Hess Scale and World Federation of Neurosurgical Societies SAH Grading Scale, whereby grades 1, 2 and 3 were deemed as 'good grades'; grades 4 and 5 as 'poor grades'.[4 5] Neurocritical care faculty members and fellows prospectively rated the initial radiological scans for: volume of subarachnoid blood using the modified Fisher Scale (mFS)[6] and Hijdra SAH score[7]; hydrocephalus; intracerebral haematoma as presence/absence of intraparenchymal blood. Volume of intracerebral haematoma was calculated by the ABC/2 method as previously described.[8] Volume of intraventricular haemorrhage was graded for each of the four ventricles on a scale of 0 (no blood) to 3 (completely filled with blood); a score was obtained by summation of each ventricle score (0–12 points).[9] Rebleeding was defined as acute worsening in neurologic status along with an increase in haemorrhage volume on a repeat CT scan.[3] In some patients, the diagnosis of SAH was based on outside hospital scans. Upon admission of these patients to Columbia University Medical Center, to rule out rebleeding, head CT was repeated if acute neurologic worsening occurred since the initial scan performed at the outside hospital.

The time of rebleeding was not recorded. Delayed cerebral ischaemia (DCI) was defined as

To cite: De Marchis GM, Lantigua H, Schmidt JM, *et al*. *J Neurol Neurosurg Psychiatry* 2014;**85**:56–59.

either symptomatic vasospasm (clinical deterioration, ie, a new focal deficit, a decrease in level of consciousness, or both) or an infarction on CT scan attributable to vasospasm. Rebleeding and DCI were adjudicated in weekly meetings of the study team after review of all relevant clinical and imaging data. Management of patients with SAH followed a prespecified algorithm, whereby systolic blood pressure above 160 mm Hg was treated with IV labetalol or nicardipine to prevent rebleeding before aneurysm securing.[10] Aneurysm securing was performed as early as feasible, and time from admission to aneurysm securing was compared between patients with and without premorbid HTN. Outcome was assessed by in-person interview or telephone structured interview at 3 months using the mRs.

Statistics

Categorical variables were compared with the Fisher test and continuous variables with the Mann–Whitney U test. We performed a logistic regression analysis to assess the association between premorbid HTN and (1) rebleeding after adjusting for known rebleeding predictors (clinical grade on admission and aneurysm size) as well as age and aneurysm location; (2) survival with good functional recovery at 3 months (mRS 0–3) and (3) mortality at 3 months, adjusting for known predictors of outcome. A p-value of ≤0.05 was considered statistically significant. All statistical calculations were made with Stata, V.12.

RESULTS

Among 1492 patients enrolled during the 16-year study period, we analysed 1312 patients with a complete past medical history and follow-up. Of these patients, 49% had premorbid HTN. Patients with premorbid HTN were more frequently women, older and non-white; more often presented in poor clinical grade, both on the Hunt & Hess and World Federation of Neurosurgical Societies (WFNS) scales; had larger volumes of cisternal and intraventricular blood; and more often had intracerebral haemorrhage on initial CT. The volume of intracerebral haemorrhage and the location of the ruptured aneurysm did not differ significantly based on premorbid HTN. Blood pressure on admission was substantially higher among patients with premorbid HTN (table 1).

The time interval between admission and securing of aneurysm did not differ between the two groups (for both groups: median interval of 1 day, IQR: 1–2, p=0.77). During hospitalisation premorbid HTN was associated with double the risk of CT-documented aneurysm rebleeding (table 2). This association remained significant after adjusting for age, admission Hunt–Hess grade, size and site of the ruptured aneurysm (adjusted OR 1.67, 95% CI 1.02 to 2.74, p=0.04) (table 2). Mean arterial blood pressure on admission did not differ significantly between patients with and without aneurysm rebleed (113 mm Hg, IQR: 97–133 vs 110 mm Hg, IQR: 94–126, p=0.09). Premorbid HTN was not associated with an increased risk of angiographic vasospasm or DCI (table 2). After adjusting for age and admission Hunt–Hess grade, premorbid HTN was associated with in-hospital renal failure, HTN and fever (table 2).

Survival with good functional recovery at 3 months (mRS 0–3) was less likely, and mortality was more likely among patients with premorbid HTN. After adjustment for age, admission, Hunt–Hess grade on admission and aneurysm size, premorbid HTN remained significantly associated with mortality (adjusted OR 1.58, 95% CI 1.04 to 2.41, p=0.03), but not with good functional recovery (table 2).

Table 1 Baseline characteristics in subarachnoid haemorrhage patients with and without premorbid hypertension

	Premorbid hypertension (n=643)	No premorbid hypertension (n=669)	p Value
Age (years)	60 (50–71)	50 (42–58)	*<0.001*
Women	450 (70.0)	427 (63.8)	*0.02*
Non-white race/ethnicity, n (%)	382 (59.4)	328 (49.0)	*<0.001*
Hunt & Hess grade, n (%)			
1, 2 or 3	409 (63.6)	505 (75.5)	*<0.001*
4 or 5	234 (36.4)	164 (24.5)	
WFNS grade, n (%)			
1, 2 or 3	369 (57.4)	480 (71.8)	*<0.001*
4 or 5	274 (42.6)	189 (28.2)	
Modified Fisher grade, n (%)			
1, no thick cisternal blood, −IVH	140 (21.8)	238 (35.6)	*<0.001*
2, no thick cisternal blood, +IVH	67 (10.4)	60 (9.0)	
3, thick cisternal blood, −IVH	272 (42.3)	243 (36.3)	
4, thick cisternal blood, +IVH	164 (25.5)	128 (19.1)	
Hijdra subarachnoid haemorrhage sum score*	17 (10–24)	14 (7–20)	*<0.001*
Intracerebral clot	128 (19.9)	88 (13.1)	*0.002*
Intracerebral clot volume (mL)	11.4 (4.2–23.6)	7.5 (3.0–20.5)	0.36
IVH sum score†	2 (0–4)	1 (0–3)	*<0.001*
Hydrocephalus	277 (43.1)	226 (33.8)	*0.001*
Systolic BP, mm Hg	167 (145–193)	142 (126–166)	*<0.001*
Diastolic BP, mm Hg	90 (79–106)	82 (70–96)	*<0.001*
APACHE-II score ‡	12 (8–20)	9 (5–16)	*<0.001*

Data are n (%) or median (IQR). Numbers in italics denote that the p-values are significant.
*Range: 0, no blood; 30, all cisterns completely filled.
†Range: 0, no IVH; 12, all ventricles completely filled with IVH.
‡Range: 0, lowest; 71, highest.
BP, blood pressure; IVH, intraventricular haemorrhage; WFNS, World Federation of Neurosurgical Societies.

Table 2 Complications and outcomes according to premorbid hypertension status

	Premorbid hypertension (n=643)	No premorbid hypertension (n=669)	p Value	OR after adjusting for age and Hunt & Hess grade on admission		
				Adjusted OR	95% CI	p Value
Neurological complications						
Aneurysm rebleeding*	76 (11.8)	37 (5.5)	*<0.001*	1.67	1.02 to 2.74	*0.04*
Hydrocephalus (treated with EVD)	277 (43.1)	226 (33.8)	*0.001*	1.05	0.79 to 1.38	0.75
Delayed cerebral ischemia	134 (20.8)	139 (20.8)	1.00	N/A		
Angiographic vasospasm	162 (25.2)	201 (30.0)	0.08	N/A		
Medical complications						
Arrhythmia	94 (14.6)	60 (9.0)	*0.005*	1.29	0.89 to 1.87	0.18
Hyperglycaemia (>11.0 mmol/L)	366 (56.9)	312 (46.6)	*<0.001*	1.20	0.95 to 1.54	0.12
Renal failure (creatinine>220 μmol/L)	35 (5.4)	8 (1.2)	*<0.001*	4.95	2.19 to 11.2	*<0.001*
Hypertension (treated with IV therapy)	366 (56.9)	299 (44.7)	*<0.001*	1.37	1.09 to 1.73	*0.008*
Fever (>38.6°C)	362 (56.3)	301 (45.0)	*<0.001*	1.32	1.04 to 1.67	*<0.02*
3 month modified Rankin scale score						
0 to 3 (good functional outcome)	373 (58.0)	495 (74.0)	*0.002*	Reference		
4 or 5 (poor functional outcome)†	117 (18.2)	97 (14.5)	*<0.001*	0.78	0.48 to 1.30	0.35
6 (death)†	153 (23.8)	77 (11.5)	*<0.001*	1.58	1.04 to 2.41	*0.03*

Data are n (%). N/A: not applicable, denoting that the adjusted OR was not calculated because of lack of statistical significance in the univariate analysis. Numbers in italics denote that the p-values are significant.
Interpretation of the OR, example: 'Patients with history of hypertension had 1.67 times higher odds of rebleeding compared to patients without history of hypertension, after adjusting for age, age, clinical severity on admission, size and location of the ruptured aneurysm.'
*Adjusting for age, Hunt & Hess Grade on admission, aneurysm rupture size and site (dichotomised into anterior circulation (carotid artery, anterior and middle cerebral artery, anterior communicating artery) and posterior circulation (posterior communicating artery, posterior cerebral artery, basilar artery, vertebral artery)).
†Adjusting for age, Hunt & Hess Grade on admission and size of the ruptured aneurysm.
EVD, external ventricular drain; IV, intravenous.

DISCUSSION

In this cohort study spanning over two decades, we found that premorbid HTN was associated with increased severity of the initial bleeding event as assessed by all measures of haemorrhage on the initial CT. Premorbid HTN was also associated with twice the frequency of aneurysm rebleeding, a risk that has not been widely recognised.

The association of premorbid HTN with more severe initial bleeding differs from a smaller study that did not confirm this association.[11] Improved quality of urgent CT scans and the use of standardised scales to estimate the amount of blood in different intracranial compartments may explain this discrepancy. Higher blood pressure at ictus, or more advanced vessel structural damage due to atherosclerotic disease, might also explain the more severe burden of haemorrhage among SAH patients with premorbid HTN.

The association between premorbid HTN and rebleed retained its significance even after statistical adjustment for admission Hunt–Hess grade and size of the ruptured aneurysm —two previously established predictors of rebleeding in our database[2]—as well as age and aneurysm rupture site. Time from admission to aneurysm securing was equally short (1 day) in patients with and without premorbid HTN, and is therefore unlikely to explain the observed difference in aneurysm rebleeding. Rebleeding occurred in 8.6% of our study cohort, and should be viewed as a distinct and preventable cause of poor outcome in SAH patients with premorbid HTN. Our findings have implications for clinical practice. First, in all patients—particularly in those with premorbid HTN —the treating staff should closely monitor and control HTN as early as possible and, at least, as long as the ruptured aneurysm is unsecured. Second, a randomised controlled trial and single-centre cohort study indicate that early antifibrinolytic therapy until definitive aneurysm repair, up to 72 h after onset, reduces the risk of rebleeding by approximately 80%.[12 13] Premorbid HTN and poor clinical grade imply a higher than average rebleeding risk, and should encourage clinicians to strongly consider this intervention whenever definitive aneurysm repair cannot be performed immediately.

Premorbid HTN was associated with an increased frequency of a variety of neurological and medical complications which most likely reflected worse clinical grade and older age in these patients. Surprisingly, premorbid HTN was not associated with an increased risk of DCI or angiographic vasospasm by contrast with other reports claiming a link.[14] It is difficult to explain why the larger amounts of cisternal blood found in hypertensive patients were not associated with DCI. One putative mechanism is that patients with history of HTN had higher in-hospital blood pressure levels that may have reduced the risk of DCI. This remains a speculative explanation because the blood pressure levels during the hospitalisation were not available for this analysis. Alternatively, the association between premorbid HTN and cisternal blood was not sufficiently strong to translate into a higher rate of DCI. Of interest, aneurysm rebleeding was not associated with DCI in a previous publication from the same team.[3] At 3 months, premorbid HTN was associated with a doubling of the mortality rate. This association remained significant after controlling for age, Hunt–Hess grade on admission and aneurysm size, the three most important baseline determinants of outcome in our database. This is in line with other studies that have linked premorbid HTN to poor outcome after SAH.[11 15] This study has limitations. First, sedative medication or intubation can influence clinical grading, and data in this regard were lacking. Yet, sedation and intubation of SAH patients followed the same prespecified algorithm,[10] so that we deem unlikely that a difference in treatment between patients with, versus without premorbid HTN, biased the reported clinical grading. Second, premorbid and in-hospital blood pressure

levels after admission were not systematically available, so that we cannot exclude that differences in the actual blood pressure may have contributed to the different rebleeding rates. The higher in-hospital use of antihypertensive medication in patients with premorbid HTN suggests indeed that their in-hospital blood pressure levels were higher. The conclusions of the study, therefore, apply only to a 'history of premorbid HTN' as elicited in the emergency department. Third, the radiological scans were rated by neurocritical care faculty members and fellows who had full access to all medical data, so that blinding to the presence of premorbid HTN cannot be guaranteed. However, the rating of the radiological scans based on the prespecified, referenced criteria and information on premorbid HTN was not routinely incorporated into imaging rating. Finally, complete medical histories were lacking in 12% of patients in this observational study (only patients with complete medical histories were included).

In conclusion, a history of premorbid HTN represents a significant risk factor for aneurysm rebleeding. Given that aneurysm rebleeding is a potentially fatal—but preventable—complication, these findings are of clinical relevance.

Contributors GMDM and SAM contributed to the conception and design of the study. All authors contributed to data collection, writing and critical review of the manuscript, and gave their final approval of the version to be published.

Funding GMDM is supported in the frame of a Career Development Grant for junior investigators (PBBEP3_139388) funded by the Swiss National Science Foundation; by a grant from the Swisslife Jubiläumsstiftung for Medical Research; by a grant from the Swiss Neurological Society; by a grant of the Fondazione Dr Ettore Balli, Ticino, Switzerland.

Competing interests SAM has received consulting fees from Actelion Pharmaceuticals.

Patient consent Obtained.

Ethics approval Institutional review board approval.

Provenance and peer review Not commissioned; externally peer reviewed.

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