Original Article

Spontaneous Intracerebral Hemorrhage in the Young: An Institutional Registry Analysis

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Abstract

Background: Spontaneous intracerebral hemorrhage (SICH) accounts for about 10–15% of all strokes. Generally, it is a disease of the elderly; worldwide, the incidence of SICH in the young is showing an increasing trend, especially in India and the Asian continent. An attempt is also made to analyze the presence of factors, which may predict the risk of SICH among young hypertensives. **Methods:** A six-year retrospective review of patients aged below 50 years who presented with SICH was included in the study. Patients with bleeds secondary to an identifiable cause such as tumor, trauma, vascular malformations, and coagulopathy-induced bleeds were excluded from the study. The outcome was measured at 90 days using the modified ranking scale, and predictors of outcome (good outcome modified ranking score (mRS): 0–3; poor outcome mRS: 4–6) were analyzed. **Results:** SICH in the young accounted for 28.4% of all intracerebral hemorrhage (ICH) patients admitted during the study period (344/1210). The mean age of our male-dominant (78.5%) cohort was 42.9 ± 6.24 years, and the median Glasgow coma score (GCS) on presentation was 11 (IQR: 8–14). A prior history of hypertension (HTN) was obtained in 51.2% (176), and left ventricular hypertrophy (LVH) was documented in 237 (68.9%) patients. The basal ganglia was the most common location of the bleed (62.2%). At 90 days, 200 patients (58.1%) had good outcome and 144 (41.9%) had poor outcome with an overall mortality of 75 (21.8%). Independent predictors of poor outcome were poor GCS, larger volume, and high serum creatinine values. **Conclusion:** The incidence of SICH among the young accounts for nearly 30% of admitted ICH. Poor outcome and mortality are high with HTN being the single most important modifiable risk factor in the cohort.

Keywords: Hemorrhagic stroke, outcome in ICH, young ICH

Introduction

Intracerebral hemorrhage (ICH) accounts for 15–20% of stroke worldwide and although less common than ischemic strokes, which carry a poorer outcome.[1] The incidence of ICH has been increasing worldwide and is reportedly more common in the Asian population.[2] In the Indian subcontinent, ICH is a disease of the young with multiple studies showing a mean age around the 6th decade (50–60 years).[3,4] This is in contrast to the Western literature where ICH is predominantly a disease of the elderly with a mean age over 70 years.[5,6] In the West, the primary causes of ICH in the young include arteriovenous malformations, cavernous angiomas, cryptogenic disease, and hypertension (HTN).[7] This is in stark contrast to the Asian population where the primary cause of ICH remains uncontrolled HTN and alcohol abuse.[8] Yet, the literature for young ICH in India is sparse and most series include ICHs with multiple etiologies.[9] Almost all series report bleeds secondary to coagulation abnormalities, vascular malformations, cerebral venous thrombosis, and tumor bleeds, and ICH series exclusive on hypertensive or idiopathic etiology are seldom reported. This study analyses a large series of young patients with spontaneous intracerebral hemorrhage (SICH) in a tertiary care center in South India and attempts to discuss the dilemmas shrouding this disabling pathology.

Methods

A retrospective review of patients enrolled in our stroke registry was performed. All patients who presented with ICH between the ages of 18 and 50 years and were admitted between January 2015 and December 2020 were included in the study. Patients with demonstrable vascular malformation, intracranial aneurysm, trauma, cerebral venous thrombosis, hemorrhagic transformation of infarct, or lesion-related hemorrhage were excluded. Demographic, clinical, biochemical, and radiological data were obtained from our online register. Radiological data were obtained from the first computed tomography (CT) scan of the patients. The site, laterality, and volume of hematoma were measured using the axbxc/2 method.[10] In patients with suspicion of vascular abnormalities, an angiogram was performed (CT angiogram/4-vessel digital subtraction angiogram) and those patients with underlying anomalies were excluded. Electrocardiogram and two-dimensional (2D) echocardiogram results were analyzed

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from case records. Left ventricular hypertrophy (LVH) was identified in electrocardiogram (ECG) using the Sokolov–Lyon criteria: S-wave depth in V1 + tallest R-wave height in V5–V6 > 35 mm.[11]

The outcome was measured using the modified Rankin 6-point outcome scale routinely used in stroke outcome measurement. The outcome at discharge was collated from discharge summaries and 90-day outcome from follow-up case records. In case the patient failed to visit the clinic, a telephonic call was made to record the outcome using the questionnaire.[12] The outcome was dichotomized as good outcome (mRS: 0–3) and poor outcome (mRS: 4–6).[4-6]

Institutional ethical clearance was obtained. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) V 26.0 for Macintosh. Descriptive analysis was performed by calculating the mean, median, and frequency tables. Univariate and multivariate logistic regression was performed to determine independent predictors of outcome.

Results

During the study period, a total of 1210 patients were diagnosed to have spontaneous intracerebral hemorrhage (SICH). After appropriate exclusions, a total of 344 patients were included in the study for analysis. It accounted for 28.4% of all ICH patients admitted to our center during the same period. The mean age of our cohort was 42.9 ± 6.24 years. The cohort was male-dominant (270, 78.5%), and the median Glasgow coma score (GCS) on presentation was 11 (IQR 8–14) with a heart rate of 83 ± 16/min. The mean systolic blood pressure (BP) on admission was 178 ± 77 mmHg, and the diastolic BP was 101 ± 17 mmHg. Only 65 patients (18.9%) had a prior history of diabetes, and the mean random blood sugar levels on admission were 160.62 ± 68.1 mg/dL. The mean serum creatinine levels were 1.2 ± 1.17 md/dL. A prior history of HTN was obtained in 176 (51.2%) of the patients. ECG and echocardiogram were suggestive of LVH in 237 (68.9%) patients. Overall, 118 patients (34.3%) had long-standing signs of HTN (LVH) without any previous history of the same.

Radiological parameters were obtained from a CT scan on admission. Of the 344 patients, 152 (44.2%) were right-sided, 165 (48%) were left-sided, 26 (7.6%) were midline, and one (0.3%) was bilateral. The bleed was of supratentorial origin in 303 (88.1%) patients and infratentorial in 23 (6.7%) patients. Basal ganglia was the most common location (214 (62.2%)), followed by lobar (45 (13.1%)), thalamus (43 (12.5%)), brainstem (16 (4.7%)), cerebellar (8 (2.3%)), and primary intraventricular (IVH) (18 (5.2%)). The median mRS on discharge was 4 (IQR: 3–5) and 3 (IQR: 2–5) at 90 days. At the last follow-up, 200 patients (58.1%) had good outcome and 144 (41.9%) had poor outcome and an overall mortality of 75 (21.8%) [Table 1].

Surgical evacuation of hematoma was performed in 74 (21.5%) patients, and an external ventricular drain (EVD) was performed in 22 (6.4%) patients. Among the surgical patients, 25 (12.5%) had a good outcome and 49 (34%) of them had a poor outcome. Similarly, in patients who underwent an EVD six (3%) had good outcome and 16 (11.1%) had poor outcome. A total of 27 (7.8%) who underwent surgical procedure were dead at 3 months. Surgical patients were of poor GCS at admission and were found to have a higher volume of clot ($P < 0.001$). Surgery did not necessarily improve outcome in these patients but increased the number of disabled survivors in this cohort ($P < 0.001$). Mortality rates computed for the ICH score were 5.3%, 9.6%, 20%, 54.1%, and 75% for scores of 0 to 4 [Table 2].

Predictors of poor outcome were analyzed using univariate and multivariate logistic regression. Heart rate, high diastolic BP, poor GCS, high blood glucose on admission, elevated serum creatinine levels, large volume of hematoma, and location were predictors of outcome in the cohort on univariate analysis ($P < 0.05$) [Table 1]. Independent predictors of poor outcome based on logistic regression were poor GCS, larger volume, and high serum creatinine values [Table 3].

Discussion

The frequency of SICH among the young varies from 0.7% to 40% among different series. A higher incidence is more often reported in India and other Asian countries compared with the West.[9,13-16] Studies on young SICH are limited and primarily revolve around a limited independent series of patients.[9,17-27]

Incidence and prevalence

The global prevalence of hemorrhagic stroke almost doubled from 1990 to 2013 in people aged 20–64 years, reaching ~3.7 million patients (95% CI: 3.5–3.9 million patients).[28] It accounts for nearly 10.0% to 38.5% of all stroke in young.[26,27,29,30] In general, the ratio of ICH to ischemic stroke ranges from 1:1.5–2.0 in young adults and 1:5.4 in individuals >75 years of age.[31] In a meta-analysis published in 2010, the incidence of ICH in people aged <45 years was 1.9 per 100,000 individuals (95% CI: 1.6–2.2) but increased by tenfold for those aged 45–54 years (19.1 per 100,000 individuals; 95% CI: 13.4–27.4) and by nearly 20-fold for those aged 55–64 years (36.5 per 100,000 individuals; 95% CI: 28.4– 46.7).[32] This incidence is higher in low-income and middle-income countries.[9,32,33] India has a high prevalence of young hypertensives below the age of 50 (20%),[16] and this along with other factors such as dietary, sociocultural, and genetic variation accounts for the higher incidence of SICH among young in India.[3,34]

Risk factors

Risk factors for SICH in young have not been well studied. Suspected factors include HTN (OR: 5.71), diabetes (OR: 2.40), menopause (OR: 2.50), current cigarette smoking (OR: 1.58), a high alcohol intake (≥2 drinks daily; OR; 2.23), a high caffeinated drink intake (≥5 drinks daily; OR: 1.73), caffeine in drugs (OR: 3.55), and drug abuse and lower serum cholesterol levels.[28,35-38] HTN remains an important

Table 1: Clinical and demographic radiological predictors of outcome

Parameter	*n*=344	Good outcome (200)	Poor outcome (144)	*P*
Age	42.92±6.24	42.97±6.19	42.85±6.32	0.87
Sex				1
Male	270 (78.5%)	157 (78.5%)	113 (78.5%)	
Female	74 (21.5%)	43 (21.5%)	31 (21.5%)	
Hypertension	176 (51.2%)	104 (52%)	72 (50%)	0.744
Duration	3.8±4	4.17±4.83	3.32±2.43	0.32
Diabetes mellitus	65 (18.9%)	41 (20.6%)	24 (16.7%)	0.4
Duration	4.1±2.1	4±1.82	4.25±2.6	0.88
GCS	11 (8-14)	12	8	<0.001
Heart rate	83±16	81.71±15.18	84±17.73	0.08
Systolic BP	178±77	175.58±112.58	181.18±35.2	0.56
Diastolic BP	101±17	98.95±16.75	103.75±17.1	0.01
Blood glucose	160.62±68.1	147.58±56.45	179.06±80.41	<0.001
Serum creatinine	1.2±1.17	1.05±0.63	1.53±1.61	<0.001
ECG/echo-LVH	237 (68.9%)	141 (71.9%)	96 (72.2%)	1
Radiological features				
Side				0.176
Right	152 (44.2%)	94 (47%)	58 (40.3%)	
Left	165 (48%)	95 (47.5%)	70 (48.6%)	
Midline	26 (7.6%)	11 (5.5%)	15 (10.4%)	
Bilateral	1 (0.3%)		1 (0.7%)	
Volume	23.15±19.73	16.44±12.28	32.47±23.95	<0.001
Supratentorial	303 (88.1%)	178 (89%)	125 (86.8%)	<0.001
Basal ganglia	214 (62.2%)	118 (63.8%)	96 (68.1%)	
Thalamus	43 (12.5%)	27 (14.6%)	16 (11.3%)	
Lobar	45 (13.1%)	33 (17.8%)	12 (8.5%)	
Infratentorial	23 (6.7%)	7 (3.5%)	16 (11.1%)	
Cerebellar	8 (2.3%)	4 (2.2%)	4 (2.8%)	
Brainstem	16 (4.7%)	3 (1.6%)	13 (9.2%)	
Primary IVH	18 (5.2%)	15 (7.5%)	3 (2.1%)	
Surgery	74 (21.5%)	25 (12.5%)	49 (34%)	<0.001
EVD	22 (6.4%)	6 (3%)	16 (11.1%)	0.003

Table 2: ICH score in the cohort

ICH score	Mortality at 3 months	Hemphill *et al*.'s 30-day mortality
0	4 (5.3%)	0
1	11 (9.60%)	13%
2	15 (20.00%)	26%
3	33 (54.10%)	72%
4	12 (75.00%) *n*	97%
5	0	100%

risk factor in our cohort with 51.2% of patients reporting it at admission and 68.9% showing evidence of HTN in the form of LVH on cardiovascular workup (electroencephalogram/echocardiogram (EEG/ECHO)). 50% of our patients were newly detected hypertensives with evidence of LVH. Undetected HTN is a large contributor to ICH in our cohort with 118 (34.3%) patients having their first diagnosis of HTN on arrival to our emergency room with a bleed. Chronic kidney disease is an established risk factor in young ICH[39] and our cohort was seen in 39 patients (11.7%). Elevated levels of creatinine ($P < 0.001$) were also found to be an independent predictor of poor outcome. Nonquantifiable factors such as stress[40,41] are known to be associated with an increased risk of ICH.

Female-specific risk factors

Pregnancy and the postpartum period are virtually the only ICH risk factors exclusive to young female individuals.[42-44] In one seminal study on this topic, the adjusted relative risk of ICH was 2.5 during pregnancy and increased to 28.3 during the postpartum period.[44] Our cohort had two patients in the peripartum period, and both were diagnosed to have pregnancy-induced HTN.

Causes of ICH

HTN and cerebral amyloid angiopathy are the most common risk factors among the elderly. Studies from several countesses in the Asia Pacific region, Taiwan, India, and South Korea.[18,24,34] have shown that there is geographic variability in the etiologies, clinical profile, and outcomes of nontraumatic ICH in the young. The first cause-based classification system for ICH was published in 2012 and included six categories: structural causes, medication, amyloid angiopathy, systemic disease, HTN, and undetermined etiology (SMASH-U). HTN seems to be the leading cause of ICH in India and among Asian populations,[9,18,34] whereas structural lesions such as arteriovenous malformations are either the leading causes of ICH[9,18,23,25,26] in the West. An age threshold of 35 years seems to represent a border zone with individuals less than 35 years of age most commonly having a structural cause and HTN being the etiology in older individuals. In our study, HTN (70%) was the most common etiology of ICH. In the remaining patients, no specific cause was found. The higher incidence of HTN in our study could be due to the inclusion of patients up to 50 years of age, exclusion of aneurysmal and vascular malformation bleeds, patients with anticoagulant usage, venous thrombosis, and a higher prevalence of HTN in the Indian population compared with the West.[45] None of our patients had ICH related to drug abuse.

Sites

In our study, deep-seated ICH constituted about three-fourths of patients, which may be due to the high frequency of HTN in our study. In the present study, 13% of ICH was lobar among which 53% were hypertensive in etiology. The frequency of cryptogenic ICH in young ranges between 4.4% and 15%.[25,35] In the present study, lobar hemorrhage had a higher GCS score at admission and good outcome at one month compared with known etiology.

Imaging

CT is the preferred mode of imaging over magnetic resonance imaging (MRI) in an emergency setting. An angiogram is indicated in young patients, those with lobar

Table 3: Independent predictors of poor outcome computed by logistic regression

Parameter	*P*	Odds ratio	95% CI	
			Lower	Upper
Volume of hematoma	0.002	1.034	1.012	1.057
Glasgow coma score	<0.001	0.697	0.627	0.775
Serum creatinine	0.018	1.478	1.069	2.042
Blood glucose	0.072	1.004	1	1.009

hemorrhage (particularly if associated with intraventricular or subarachnoid hemorrhage), and those without a history of HTN or coagulopathy.[46-48] It is a common clinical dilemma as to which group of patients needs repeat angiography when the findings of comprehensive initial imaging studies are nondiagnostic.[48] It is preferable to repeat vascular imaging in non-hypertensive patients at 6–12 weeks after clot resolution to avoid missing out on small vascular lesions, which may be masked due to the mass effect of the hemorrhage.

Outcomes

Most deaths seem to occur during the first few weeks after ICH and are attributable to neurological complications. In various studies, in-hospital mortality ranged from 12.5% to 34.1% and one-month mortality from 8.1% to 26.1%.[18,21,22,25,28,35,49] Mortality in our study was 21.8%. Mortality rates for the ICH score were lesser compared with the rates quoted by Hemphil *et al*.[6] in their landmark paper. This has been a consistent finding in our studies (quote), and one of the factors responsible was younger age.[3] Independent factors associated with early mortality include female sex, poor GCS, large clots, infratentorial hematoma location, multiple hemorrhages, high leukocyte count, hyperglycemia, comorbidities, and structural cause of ICH.[9,17,18,34] In our study, hematoma volume, GCS, and serum creatinine were independent predictors of mortality. Studies from Asian centers report high mortality probably related to low socioeconomic status and comorbid vascular conditions.[9,17] Recurrence of ICH is seen in patients with poor compliance with medications. Two early studies conducted in Mexico and Ecuador found high ICH recurrence rates in young patients up to 9.0%.[19,20] The Finnish[17,50] and Dutch[24] studies described above showed similar cumulative risks of recurrent ICH at 10 years (11.2% and 12.2%), especially in patients with an underlying structural cause. In our cohort, five (1.45%) patients were admitted to our center with recurrent ICH in a secondary location during the study period. All were found to be due to poor compliance with antihypertensive medications.

Functional outcome

Good outcome (Glasgow Outcome Scale score of 4–5 or a modified Rankin Scale score of 0–2) is limited to 34.9%–39.9% at discharge or at 1 month after ICH.[9,17,24] Higher age, increasing initial National Institutes of Health (NIH) Stroke Scale (NIIHS) scores, intraventricular extension, and hypertensive ICH are predictors of poor outcome.[24,34] In our study, good outcome (mRS: 0–3) at three months was achieved by 58.1% of our patients, in comparison with 45.53% in our larger series of adult and young patients.[34] Compared with ischemic stroke in young patients, ICH in young patients carries an increased risk of poor functional outcome in the long term.[51]

Limitations

This study is a retrospective study from a prospectively maintained ICH register at our institute. This study included only patients attending our hospital. Information regarding patients' history was obtained from bystanders, most commonly first-degree relatives in the absence of national centralized health records. The GCS score was used for the initial assessment of patients rather than the NIIHS score. Only 90-day outcomes are available, and longer follow-up would be beneficial considering the young cohort.

Conclusions and Future Perspectives

SICH in the young is on the rise, especially in developing countries like India. Undetected HTN remains a major modifiable risk factor, but the exact etiology remains elusive in a significant group of patients. Outcomes are generally poor in patients with large bleeds, who present in a poor neurological state. The need for further research on nonquantifiable risk factors such as stress and sympathetic overdrive cannot be overemphasized. Prevention remains the key, and national programs should prioritize timely detection of HTN in the young.

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Conflicts of interest

There are no conflicts of interest.

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