

Brainstem hemorrhage is uncommon and is associated with high morbidity, mortality, and prolonged hospitalization

Renad M. AlMohammedi, MBBS, Hadeel AlMutairi, MBBS, Rana O. AlHoussien, MBBS, Malack T. AlOtayan, MBBS, Abeer K. AlMutairi, MBBS, Wejdan O. Bafail, MBBS, Altaf Khan, MS, Ismail A. Khatri, MD, FAAN.

ABSTRACT

الأهداف: تحديد انتشار وعوامل الخطر ونتائج مرضى نزيف جذع الدماغ في مركز السكتة الدماغية بمدينة الملك عبدالعزيز الطبية بالرياض.

المنهجية: أجريت دراسة استيعابية للمجموعة على جميع المرضى الذين يعانون من نزيف جذع الدماغ خلال الفترة من يناير 2014م إلى ديسمبر 2017م. حللنا كلاً من العرض السريري وموقع النزيف والمضاعفات والنتائج السريرية.

النتائج: من بين 1921 مريضاً بالسكتة الدماغية، كان 219 منهم مصابين بالسكتة النزفية (11.4%)، منهم 10 فقط (4.6%) لديهم نزيف في جذع الدماغ، بما في ذلك 0.5% من جميع مرضى السكتة الدماغية. جميع المرضى من الرجال. كان متوسط العمر 58.5 سنة. كانت الأعراض الأكثر شيوعاً هي الصداع (70%) والضعف الأحادي (60%) وفقدان الوعي (50%). كان جميع المرضى يعانون من نزيف في الأضواء، وكان 5 منهم مصاحباً لنزيف في المخيخ (50%)، وكان أحدهم يعاني من نزيف في النخاع، ونزيف في الدماغ المتوسط (10% لكل منهما). كان متوسط مدة الإقامة في وحدة العناية المركزة 17 يوماً؛ يعني أن الإقامة في المستشفى كانت 58 يوماً. في وقت التفرغ، كان لدى ثلاثة (30%) mRS من 0-2، و 5 (50%) كان لديهم mRS من 3-5، بينما مات 2 (20%). ارتبط مقياس غيبوبة غلاسكو (GCS) من <8 عند العرض بنتيجة جيدة عند ثلاثة أشهر (p=0.03). العرض خلال ست ساعات من ظهور الأعراض (p=0.233)، ارتفاع ضغط الدم عند التقديم (p=0.233)، والعمر أقل من 60 سنة (p=0.065) لم يؤثر على نتائج التفرغ.

الخلاصة: حدث نزيف في الدماغ في 0.5% من جميع مرضى السكتة الدماغية. كان مرتبطاً بارتفاع معدلات المراضة والوفيات. ارتبط مقياس غلاسكو غيبوبة المنخفض في العرض التقديمي بالنتائج الضعيفة

Objectives: To determine the frequency, risk factors, and outcomes of patients with brainstem hemorrhage in stroke center at King Abdulaziz Medical City, Riyadh.

Methods: A retrospective, observational cohort study including all patients with brainstem hemorrhage from January 2014 to December 2017. The clinical presentation, location of hemorrhage, complications and clinical outcomes were analyzed.

Results: Of 1921 stroke patients, 219 had hemorrhagic stroke (11.4%), of whom only 10 (4.6%) had brainstem hemorrhage, comprising 0.5% of all stroke patients. All patients were men; mean age was 58.5 years. Most frequent presenting symptoms were headache (70%), unilateral weakness (60%), and loss of consciousness (50%). All patients had hemorrhage in pons, 5 had concomitant cerebellar hemorrhage (50%), one had medullary hemorrhage, and one midbrain hemorrhage (10% each). Mean ICU stay was 17 days; mean hospital stay was 58 days. At the time of discharge, three (30%) had mRS of 0-2, 5 (50%) had mRS of 3-5, whereas 2 (20%) had died. Glasgow coma scale (GCS) of >8 at presentation was associated with a good outcome at three months (p=0.03). Presentation within six hours of symptom onset (p=0.233), hypertension on presentation (p=0.233), and age less than 60 years (p=0.065) did not affect discharge outcomes.

Conclusion: Brainstem hemorrhage occurred in 0.5% of all stroke patients. It was associated with high morbidity and mortality. Low Glasgow Coma Scale at presentation was associated with poor outcomes.

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From the Division of Neurology (AlMohammedi, Khatri), Department of Medicine, King Abdulaziz Medical City, College of Medicine (AlMutairi H, AlHoussien, AlOtayan, AlMutairi A, Bafail, Khatri), King Saud bin Abdulaziz University for Health Sciences, and from King Abdullah International Medical Research Center (Khan, Khatri), Riyadh, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Ismail A. Khatri, Division of Neurology, Department of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Kingdom of Saudi Arabia. E-mail: ismailkhatri@yahoo.com
ORCID ID: <https://orcid.org/0000-0002-0218-18>



Stroke is among the leading causes of death and disability worldwide. In 2013, stroke was the second most common cause of death, accounting for 11.8% of all deaths worldwide, second only to ischemic heart disease.¹ In Saudi Arabia, the reported prevalence of stroke is low compared to the Western countries, probably due to the predominance of a younger population in this region. One early study reported that the crude incidence of first-ever stroke in Saudi Arabia was 29.8/100,000/year, whereas the standardized incidence was 125.8/100,000/year.² Stroke is pathologically classified into ischemic stroke, and hemorrhagic stroke. Ischemic stroke includes cerebral, retinal and spinal infarction, whereas hemorrhagic stroke typically includes intracerebral hemorrhage and subarachnoid hemorrhage.³ Intracerebral hemorrhage frequency ranges from 6.5% to 19.6% of all strokes and is associated with high mortality.^{4,5} Intracerebral hemorrhage (ICH) is mostly caused by the rupture of arteries due to hypertensive changes or other vascular abnormalities.⁶

The incidence of hypertensive ICH has decreased in the developed countries with better blood pressure control, whereas the burden of ICH has increased in the developing countries.^{4,7} In an analysis of 500 consecutive cases from a hospital-based study in Saudi Arabia, ICH was detected in 21.4%.⁸ Brainstem hemorrhage is an uncommon form of ICH. In one study, 60 of 1033 patients with ICH were diagnosed with pontine hemorrhage – an incidence of 5.8%.⁹

The outcome for ICH is variable, depending on the age, use of anticoagulants, volume or expansion of hematoma, and extension to ventricles.¹⁰ ICH has higher mortality and disability than ischemic stroke.¹¹ Only 12% to 39% of patients with ICH have a good prognosis.¹¹ In a meta-analysis of 122 eligible studies, it was found that less than a third of patients with ICH survive 5 years and less than half of them survive one year.¹² In Saudi Arabia, 31% of stroke patients died as an eventual outcome.¹³ Moreover, in this Saudi study, stroke patients had an average hospital stay of 63 days.¹³

There is a lack of Saudi Arabian studies about the frequency and outcome of stroke.¹⁴ These kinds of studies have a great impact on understanding the disease and improving the health care practice and awareness.¹⁴

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We found some local studies that studied frequency and subtypes of stroke including brainstem hemorrhage, but were not specific to brainstem hemorrhage.^{8,13} The pattern of each subtype was not clear in the mentioned studies. They lack the specificity of studying brainstem hemorrhage, its clinical presentation, the outcomes, and the complications. So, this study aimed to determine the frequency and the risk factors of brainstem hemorrhage among all adult stroke patients. It also investigated the in-hospital complications and the clinical outcomes at discharge and at 3 months.

Methods. The study was approved by the Institutional Review Board (IRB) of King Abdullah International Medical Research Center (KAIMRC). It was conducted in the stroke unit of the King Abdulaziz Medical City (KAMC), Ministry of National Guard Health Affairs (MNGHA), in Riyadh, Saudi Arabia. It was a retrospective, observational cohort study from January 2014 to December 2017. The IRB waived the need for consent from patients due to retrospective chart review nature of the study. Brainstem hemorrhage, hemorrhagic stroke, intracerebral hemorrhage, and Saudi Arabia were used as key terms to search local studies about brainstem hemorrhage from various databases including PubMed, google scholar, Research Gate, as well the Saudi Ministry of Health Open Data.¹⁵

Inclusion/exclusion criteria. All patients above the age of 16 years, of both genders, with a final diagnosis of brainstem hemorrhage were included. Patients with ischemic stroke and with hemorrhagic stroke primarily outside the brainstem were excluded. Patients with other types of brain hemorrhage, for example, subdural hemorrhage and subarachnoid hemorrhage, were also excluded. Brainstem hemorrhage was defined as any hemorrhage where the epicenter of the hemorrhage was considered to be in the brainstem (midbrain, pons, medulla) or in the cerebellum with involvement of any part of the brainstem. Patients with intracerebral hemorrhage but without involvement of the brainstem were excluded. Patients with intracerebral hemorrhage in whom the involvement of the brainstem was an extension of the ICH from other locations were also excluded. All brainstem hemorrhage etiologies were included except where subarachnoid hemorrhage was the primary mechanism. Intensive care unit (ICU) and hospital stays were recorded, and in-hospital complications were identified. Outcome was determined at discharge and at three months using the modified Rankin Scale (mRS) score. The mRS was determined by neurologists or residents and fellows in neurology

Table 1 - Frequency of presenting symptoms among patients with hemorrhagic stroke. N=10

Symptoms	n (%)
Unilateral weakness	6 (60)
Unilateral numbness	2 (20)
Loss of speech	3 (30)
Loss of consciousness	5 (50)
Altered level of consciousness	2 (20)
Sudden vertigo	1 (10)
Sudden balance problems	1 (10)
Sudden severe headache	7 (70)
Seizure/fit	2 (20)
Vomiting	2 (20)

Table 2 - Frequency of stroke related complications. N=10

Complications	n (%)
Seizures	2 (20)
Pneumonia	2 (20)
Urinary tract infections	4 (40)
Sepsis	2 (20)
Bedsore	1 (10)
Gastrostomy tube placement	2 (20)
Tracheostomy tube placement	3 (30)
Limb contractures	1 (10)
Death	2 (20)

training during direct patient contact.

The data were analyzed using SAS version 9.4. Descriptive statistics were presented as frequencies and percentages for categorical data. Numerical data were presented by means and standard deviations. The Pearson chi-square test was utilized to analyze the associations. *P*-value less than or equal to 0.05 was considered statistically significant.

Results. A total of 1921 patients were admitted to the stroke unit during the period January 2014 to December 2017; of these, 219 patients had hemorrhagic stroke (11.4%). Among the patients with hemorrhagic stroke, only 10 patients had brainstem hemorrhage (4.6% of all hemorrhagic strokes, and 0.5% of all strokes). All patients with brainstem hemorrhage were men, the mean age was 58.5±13.1 years and the mean BMI was 27.8±6.2 kg/m². Half the patients were younger than 60 years. Two patients were brought to the hospital by ambulance, 6 patients by private transport, and 2 patients were transferred from another hospital.

Six of the 10 patients presented within 6 hours of symptom onset, whereas 2 presented more than 24 hours after symptom onset. The most frequent presenting

symptoms are shown in **Table 1**. Common vascular risk factors included hypertension in 90%, diabetes in 80%, congestive heart failure in 30%, ischemic heart disease in 20%, prior stroke and smoking in 30% each, and dyslipidemia in 10%. One patient (10%) was on anticoagulation medication and one patient (10%) had valvular heart disease. Five (50%) patients had GCS below 8 at the time of presentation. Seven (70%) patients had focal weakness, one (10%) had focal numbness, 3 (30%) had absent brainstem reflexes, and 5 (50%) patients had pupillary abnormality. More than half (60%) of the patients presented with BP >160/100 mm Hg. Nine patients had a high blood glucose reading (90%), and the HbA1c ranged between 6.1% and 11.6%, with a mean of 6.4%.

Hemorrhagic stroke related complications are shown in **Table 2**. When evaluating the anatomical distribution of the brainstem hemorrhage, all the 10 patients had hemorrhage in pons, 5 (50%) had concomitant cerebellar hemorrhage, one (10%) had medullary hemorrhage, and one (10%) had midbrain hemorrhage. Three (30%) had intraventricular extension of the hemorrhage.

The mean ICU stay of patients with brainstem hemorrhage was 17±34 days; while the mean length of hospital stay was 58±71 days. Half of the patients (50%) were discharged home, one patient (10%) was discharged to an inpatient rehabilitation center, one patient (10%) was discharged to a long-term facility/nursing home, and one patient (10%) was still admitted at 3 months. There was no statistically significant difference in the discharge disposition between the patients below 60 years of age and those above 60 years of age (*p*=0.06) The relationship of age, durations of symptoms and presentation Glasgow Coma Scale (GCS) to discharge disposition is shown in **Table 3**.

Discussion. Brainstem hemorrhage is an uncommon type of hemorrhagic stroke. Our study looked at the frequency and clinical outcomes of brainstem hemorrhage in a local population. Among all stroke patients, only 0.5% had brainstem hemorrhage. Among the patients with hemorrhagic stroke, only 4.6% had brainstem hemorrhage. This frequency, although very low, was not totally unexpected as other studies have shown a similar low prevalence of brainstem hemorrhage.^{9,16}

Pontine hemorrhage was the most common brainstem hemorrhage, found in all ten patients. Only 10% of the patients had concomitant midbrain hemorrhage, 10% had medullary hemorrhage, 50%

Table 3 - Comparative analysis according to the age, duration of symptoms, and Glasgow Coma Scale.

Outcomes	Age			Duration of symptoms			Glasgow Coma Scale			
	< 60 years	>60 years	<i>P</i> -value	<6 hours	>6 hours	<i>P</i> -value	<8	8-12	13-15	<i>P</i> -value
Discharge disposition										
To home	20%	80%	0.06	50%	50%	0.15	20%	75%	100%	0.31
To inpatient rehabilitation	20%	0		0	25%		0	25%	0	
To long term facility/nursing home	0	20%		16.7%	0		20%	0	0	
Admitted at 3 months	20%	0		0	25%		20%	0	0	
Dead	40%	0		33.3%	0		40%	0	0	
<i>Modified Rankin scale at discharge</i>										
0 – 2	20%	40%	0.19	16.7%	50%	0.23	0	75%	0	0.05
3 – 5	40%	60%		50%	50%		60%	25%	100%	
6 (death)	40%	0		33.3%	0		40%	0	0	
<i>Modified Rankin scale at 3 months</i>										
0 – 2	0	20%	0.13	0	25%	0.16	0	25%	0	0.03
3 – 5	20%	60%		50%	25%		60%	0	100%	
6 (death)	40%	0		33.3%	0		40%	0	0	
No follow up	40%	20%		16.7%	50%		0	75%	0	

P-value of < 0.05 was considered significant

had cerebellar hemorrhage, and 30% had ventricular extension. These findings were consistent with prior observations of a higher frequency of pontine and cerebellar hemorrhage relative to other parts of the brainstem.¹⁷ A study looking at cerebral microbleeds and ICH among 79 patients with vertebrobasilar dolichoectasia found that only two of the patients had microbleeds in the medulla oblongata and 6 of them had microbleeds in the pons.¹⁷

All brainstem hemorrhage patients in our cohort were men, with a mean age of 58.5±13.1 years. Male gender and older age are considered risk factors for hemorrhagic stroke, including brainstem hemorrhage. Other studies, including a systemic review, have found male gender to be a risk factor for hemorrhagic stroke.^{1,16,18} In a study conducted in Japan, it was shown that patients with pontine hemorrhage were older in age.¹⁶ This study¹⁶ also found that older age was related to poor outcomes and high mortality, while our results showed no significant relation between age and outcomes. We suggest that this difference was possibly due to the small size of our cohort.

The mean BMI of our patients was 27.8±6.2 kg/m², which categorizes most of our patients as obese. This may suggest a correlation between higher BMI and brainstem hemorrhage. A prior study looking at the relationship

between BMI and strokes in general, suggests that high BMI is a risk factor for both hemorrhagic and ischemic strokes.¹⁹

Among the vascular risk factors, hypertension was found in 90% of our patients, which is a typical risk factor for hemorrhagic stroke; however, most studies of hemorrhagic stroke report a much smaller frequency of hypertension.¹⁸ This high number may be due to the very small sample. In our cohort, 30% of the patients had previous strokes. Diabetes mellitus was found in 8 out of our 10 patients, which accounted for a large majority (80%) as compared to the usual frequency of about 30% in stroke patients. This again may be related to the small sample with high vascular comorbidities.

At the time of presentation, 60% of the patients had blood pressure above 160/100 mm Hg, 50% had a GCS score <8, and 70% presented with a focal weakness. High blood pressure, low GCS score, and focal weakness have all been reported to be common at the time of presentation of hemorrhagic stroke.²⁰ We found that low GCS scores were significantly related to high morbidity at the time of discharge and at 3 months. This association was consistent with a study conducted in Japan that showed that low GCS is a predictive factor for poor outcomes in patients with pontine hemorrhage.¹⁶

In our cohort, all the patients developed one or more stroke related complications including seizures, hospital acquired pneumonia, urinary tract infection, sepsis, tracheostomy tube placement, and two patients died. In addition to these complications, the length of both the ICU stay and the hospital stay were prolonged for all patients. The mean length of ICU stay was 16.8 days, while the mean length of hospital stay was 58 days. According to Chan et al,²¹ the definition of a prolonged ICU length of stay is equal to or more than 10 days, which indicates that nearly half of our patients (40%) had a prolonged ICU length of stay. The patients with brainstem hemorrhage had significant disability and were not considered candidates for inpatient rehabilitation, whereas families were reluctant to take these patients home due to limited support services available at home to take care of these dependent patients. This may have contributed significantly to the prolonged hospitalization in our patients.

Our study showed that brainstem hemorrhage had very low frequency among all strokes, as well as among hemorrhagic strokes, and was associated with many complications and morbidity. It also showed that a low GCS score at time of presentation was associated with a poor outcome. Some of the strengths of our study included its large cohort, of almost 2000 stroke patients over 4 years, from January 2014 to December 2017. We looked at presentation, anatomical location, in-hospital complications, and outcomes. Follow-up at 3 months was available for most patients.

One of the major limitations of our study was its retrospective nature as this limited the interpretation of causality. Due to the small number of patients with brainstem hemorrhage, a number of associations could not be tested statistically. Incomplete documentation in charts also limited the data collection to some extent.

Conclusions and recommendations. Our study showed that brainstem hemorrhage was a very infrequent type of intracerebral hemorrhage. It was found in only 0.5% of stroke patients. It was associated with poor outcomes and high complication rates. Low GCS at presentation was a determinant of poor outcomes. Men were exclusively affected in our study, while age did not make a difference to outcome. The majority of our patients had a long intensive care unit stay and a mean length of hospital stay. Our findings add to the knowledge and pool of information about brainstem hemorrhage. Our study confirms the rarity and the poor prognosis, and confirms the association between low GCS and the outcome. Longer duration of study, or multicenter studies, could increase the cohort

size for this extremely uncommon but potentially life-threatening and disabling type of hemorrhagic stroke and help understand brainstem hemorrhage better in Saudi Arabia.

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