Cerebrovascular Accident and Snake Envenomation: A Scoping Study

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Abstract

Background: Snake envenomation is associated with serious complications including infections, bleeding and, in rare occasions, thrombosis. Previous work by our group examined the association of snakebite and acute myocardial infarction. In this systematic review we aim to assess the clinical characteristics and outcomes of acute cerebrovascular accidents that are reported to be extremely rare complications of snake envenomation.

Methods: We performed a literature search for reports on stroke associated with snake envenomation between Jan 1995 to Oct 2018, and summarized their characteristics.

Results: Eighty-three published cases were reviewed. 66.3% of the cases were younger than 50 years of age. The mean time for the onset of the symptoms is 23.8±10.9 hours after exposure. 77.1% of the cases found to have ischemic stroke, 20.5% with intra-cranial hemorrhage and both infarction and hemorrhage in 2.4%. Mortality was reported in 16.9% with mean time between onset of the symptoms and death is 4.2 days.

Conclusion: Stroke secondary to snake envenomation is a rare but serious complication. Once stroke is suspected, initiating appropriate management is crucial in reducing morbidity and mortality associated with this potentially fatal complication of snake envenomation.

Keywords

Snake Envenomation; Stroke; Cerebrovascular accident

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Competing Interests
The authors declare no competing interests.
Introduction

Snake bite is one of the causes of stroke that has been reported less frequently. According to WHO, annual rate of snake bites have been estimated 5.4 million worldwide. Proximately 81,000–138,000 deaths have been reported annually. Most common affected population is among young adults and children in Africa, Asia and Latin America [1]. According to Center of Disease Control (CDC), annual rate of snake bite in the United States is 7,000–8,000 with about 5 deaths. The most common species in the United States reported by Central of Disease Control (CDC) includes rattlesnakes, copperheads, cottonmouths/water moccasins, and coral snakes [2]. In a Sri Lanka case series, the incidence of post-bite ischemic stroke was reported 9 in 500 bites [3].

Different Snake venoms contain different types of enzymes such as phospholipase A2, acetylcholinesterase, hyaluronidase, and metalloproteinases; such enzymes that have either direct neurotoxic or procoagulant or anticoagulation effects [4]. Therefore, These enzymes predisposing for causing either cerebral infarction due to cerebral hypoperfusion (watershed infarct), thrombotic occlusion of large vessels, vasculitis, consumption coagulopathy, or cardiogenic brain embolism; or hemorrhagic stroke [5,6].

Depending on the enzyme content in the venom, the pro-coagulation versus anticoagulation activities can be prominent. For Instance, viper and colubrid venoms contain metalloproteinases, serine proteases, and C-type lentins with either agonist or antagonist platelet aggregation activity while the venom of elapids contains phospholipase A2 and three-finger proteins, which acts as an neurotoxins in neuromuscular junction [7].

There are few case series reporting snakebite related strokes with detailed information regarding the type of the venom and the type of stroke. Previous work by our group examined the association of snakebite and acute myocardial infarction [8]. In this study, we reviewed different case reports and series of snake envenomation associated with stroke and the outcome.

Methods

On October 2018, a systematic search was conducted using PubMed and Google Scholar to review case reports about stroke caused by snake envenomation from January 1995 to October 2018. Studies that listed the keywords “snake, envenomation, stroke, cerebrovascular accidents” were used to identify case reports of stroke associated with snake envenomation. The reference list of each report was checked for additional cases. Data reviewed included demographic data, cardiovascular risk factors, snake species, computed tomography of the head, magnetic resonance of the head, time of presentation, complications, management, and outcome.

Results

83 cases were identified (Table 1) [9–79]. The patients were in the age group of 5 to 80 years and the mean age was 40 ± 17.5 years, median age was 40 years and 66.3% of the cases were younger than 50 years of age. 68.7% of the cases were reported for males and 31.3%
for females. Diabetes Mellitus and hypertension were reported only in 2 cases (2.4%). Snake Species are represented in (Figure 1); however, about 30% of the cases did not mention snake species. 30% of the cases reported with Daboia, Russell’s viper, species. 83.1% of the cases were bitten in their legs and 16.9% were bitten in hands. All the cases were managed by anti-snake venom, in 27.7% of the cases the symptoms started after receiving anti-snake venom. 19.3% of the cases also treated with antiplatelet and 3.6% were treated with craniotomy. The mean time for the onset of the symptoms is 23.8±10.9 hours after exposure. 77.1% of the cases found to have ischemic stroke, 20.5% with intra-cranial hemorrhage and both infarction and stroke in 2.4%.

Complications were reported in many cases: Altered mental status necessities intubation in 36.1% of the cases, acute kidney injury was reported in 12.2%, pulmonary edema in 3.6%, myocarditis in 1.2% and endocarditis in 1.2%. The outcome of the cases showed full recovery in 26.5% with mean time needed for recovery 88.9 days. Mortality was reported in 16.9% mainly due to complication of stroke with mean time between onset of the symptoms and death is 4.2 days.

Discussion

Venomous snakes can cause stroke due to either their neurotoxic or hemotoxic enzymes [4]. However, type of stroke either hemorrhagic or ischemic depends on the venom enzyme-make up in each different snake species.

Ischemic strokes were 77.1% of the cases while ICH were 20.5%. As reported, the most common species were Russell’s vipers with higher incidence of ischemic stroke than intracranial hemorrhage (ICH). Whereas, reportedly Bothrops species were the second most common venoms to be reported with significantly more propensity towards ICH than ischemic stroke [3]. Most of the cases exposed to snake bites are young males <50 years old. Mortality rate was higher among Russell’s vipers; however, Russell’s vipers were the most commonly reported bite. There was single report of bite by Horned viper and Pseudonaja textilis with ICH; Cerastes and Deinagkistrodon envenomation were associated with large infarcts [29,74,32,66].

The venom of Bothrops species contains metalloproteinases, type of hemotoxin that can cause hemolysis, thrombocytopenia, disseminated intravascular coagulation [76,77]. Among Bothrops, ICH was frequently reported in jararacussu, atrox, marajoensis species and infarcts was reported for lanceolatu species. Most of the patient who had bites were young and no comorbidity or risk factor for either hemorrhagic or ischemic stroke except 2% who had history of diabetes mellitus or hypertension.

Mortality was more common among those who either arrived in coma or required intubation due to AMS during the course of hospitalization. Death happened within the first 4.2 days after the exposure. Risk of mortality was amplified by ICH, bilateral extensive cerebral, cerebellar infarction, mass effect, or post circulation occlusion.

However, all the cases received anti-venom once they sought medical care after exposure; while mean time for the onset of symptoms was 23.8 h after envenomation. In 27.7% of the
cases symptoms started even after receiving antivenom which indicates the potency of the venom in causing stroke and the importance of early administration of anti-venom serum with consideration of other adjutant therapies. There are some animal studies indicating the critical and time sensitive usage of metalloproteinase inhibitors and antivenom would be the best approach to reduce hemorrhagic stroke after Bothrops species envenoming [78]. Studies have shown that single individual fractions of different venoms have failed to be lethal to mice in some studies even after 48 h, whereas a corresponding concentration of whole crude venom have been sufficiently lethal within 10 min. Synergistic action of venom component is important for designing more effective antivenoms [79]. In figure 2, we summarized the postulated mechanisms for cerebrovascular accidents following a snake envenomation.

Limited access to antivenom and also lack of awareness for seeking medical management shortly after snakebite to reduce the chance of cerebrovascular events and the other complications mainly in developing countries is an alarming medical emergency to be addressed. Therefore, WHO considered snake envenomation as category A neglected tropical diseases to maximize the efforts facing its complication [80].

Conclusion

Stroke is a rare but rather serious complication of snake envenomation that is associated with high mortality rate. Further research is needed to elucidate the mechanisms of stroke in the context of snakebites thus paving the way for the development of specific therapeutic interventions. However, early administration of anti-venom serum with consideration of other adjutant therapies is crucial in snakebites in order to reduce the associated complications including strokes.

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Figure 1:
Frequency of Stroke envenomation by species. Note: 30% of the cases had no information regarding snake species.
Figure 2:
Postulated mechanisms for cerebrovascular accidents following a snake bite.
Table 1:

Cases reported with snake envenomation associated with stroke [9–78].

| Name/Year      | Age/Sex | GCS | Symptoms                        | Onset (hours) | Affected area on CT/MRI                      | Outcome (Days) |
|----------------|---------|-----|---------------------------------|---------------|----------------------------------------------|----------------|
| Sahoo AK, 2018 | 36/M    | 6   | Rt H, aphasia                   | 18            | Lt MCA                                       | Full Recovery  |
| Sahoo LK, 2018 | 36/M    | 8   | Rt H, aphasia, O               | 1             | Lt frontotemporal, Rt basal ganglia, Rt thalamus, occipital, cerebellum | Sequalae       |
| Kutiyal, 2018  | 26/M    | 6   | Locked-in syndrome             | 2             | bilateral frontal lobes                      | Full Recovery  |
| Pothukuchi, 2018 | 55/M  | 15  | expressive aphasia              | 1             | Lt parieto-occipital ICH                     | Full Recovery  |
| Bakare, 2018   | 27/M    | 15  | seizures, Rt H                 | 2             | Lt capsuloganglionic                         | Full Recovery  |
| Pothukuchi, 2017 | 70/M  | 15  | Rt H, seizures                  | 96            | Lt capsuloganglionic                         | Full Recovery  |
| Raghunayaka, 2017 | 43/M  | 9   | Rt H, seizures                  | 0.75          | Lt ICH, sub falcine herniation               | Death [11]    |
| Delgado, 2017  | 58/M    | 8   | Lt H, seizures                  | 4             | Rt nuclo-capsular ICH                        | Sequalae       |
| Oliveira, 2017 | 59/F    | 3   | coma                            | 3.5           | SAH, ICH                                     | Death [3]      |
| Janardanaarthala, 2017 | 38/F | 6   | coma, abulia                    | 2.5           | Lt capsuloganglionic, cerebellum             | Sequalae       |
| Swati, 2017    | 80/M    | 15  | Lt H                            | 2             | ICH Rt parietal, occipital/Lt PICA           | Sequalae       |
| Paul, 2017     | 75/M    | 10  | Rt H, P                         | 24            | bilateral cerebellar, Rt temporooccipital   | Sequalae       |
| Krishna, 2017  | 30/F    | 15  | seizures, Rt H                 | 4             | Lt capsuloganglionic                         | Full Recovery  |
| Pal, 2017      | 21/M    | 0   | Lt H, facial palsy              | 48            | Rt MCA                                       | Sequalae       |
| Abdul Jalal, 2017 | 48/M  | 13  | Lt H, P                         | 1             | ICH Lt frontal, temporal                     | Full Recovery  |
| Canhas, 2016   | 48/F    | 8   | Coma, hypotonia, P              | 96            | Basilar artery                               | Death [3]      |
| Silveira, 2016 | 52/M    | 13  | dizziness                       | 24            | ICH                                           | Full Recovery  |
| Ajit, 2016     | 30/F    | 15  | Lt H, facial palsy, aphasia     | 48            | Lt fronto-tempo-parietal                     | Sequalae       |
| Prabh, 2016    | 45/F    | 3   | coma, Lt H, P                   | 3             | bilateral cerebellum, thalami, frontal and parietal, Rt temporal, midbrain | Sequalae       |
| Jeyaraj, 2016  | 28/F    | 15  | P, O, facial palsy, Lt H        | 4             | Bilateral cerebellar, midbrain, left thalamic with ICH | Full Recovery  |
| Ghezala, 2015  | 37/M    | 6   | O, decerebration, rigidity      | 4             | Subdural hematoma, ICH                       | Death          |
| Pardal, 2015   | 10/M    | 15  | Rt H                            | 25            | ICH Rt frontal                               | Sequalae       |
| Gunchan, 2014  | 36/M    | 7   | Rt, coma                        | 24            | basilar artery                               | Sequalae       |
| Sex | Age | Symptoms                                                                 | Lesion                                                                 | Outcome                      |
|-----|-----|--------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------|
| M   | 40  | Broca’s aphasia                                                         | superior division of Lt MCA with ICH                                   | Sequalae                     |
|     |     |                                                                          |                                                                        |                              |
| M   | 32  | coma                                                                    | frontal, temporal, parietal                                            | Death [5]                    |
| F   | 5   | coma                                                                    | Rt frontal temporo-parieto-occipital                                  |                              |
| M   | 51  | coma, Rt H                                                              | bilateral internal capsules                                            |                              |
| F   | 32  | coma                                                                    | frontal, temporal, parietal                                            |                              |
| M   | 50  | Aphasia, Rt H, facial palsy                                             | Rt frontal, Lt parietal, Lt occipital                                 | Death [3]                    |
| M   | 17  | Facial palsy, Lt H                                                      | Rusylvian, Rt cerebellum, bilateral frontal, occipital                 | Sequalae                     |
| M   | 58  | bilateral homonymous hemianopia                                          | Bilateral occipital                                                    | Sequalae                     |
| F   | 32  | Rt H                                                                    | Lt MCA, Lt ACA, Lt ICA                                               | Sequalae                     |
| F   | 16  | Rt H                                                                    | Lt tempiro-parietal                                                   | Sequalae                     |
| M   | 16  | top-of-the-basilar syndrome                                              | ICH Lt parietal                                                       | Sequalae                     |
| M   | 65  | Aphasia, Rt H                                                           | Lt precentral, post-central, hemipons, cerebellum                      | Sequalae                     |
| F   | 27  | Germsmann’s syndrome, P                                                 | Lt parietofrontal, Lt lateral sinus thrombus                           | Sequalae                     |
| M   | 72  | Aphasia, Lt hemianopsia                                                | Lt occipito-temporoparietal                                           | Full Recovery                |
| M   | 32  | aphasia, Rt H                                                           |Lt MCA                                                                  | Sequalae                     |
| M   | 55  | Coma                                                                    | bilateral thalamic                                                    | Sequalae                     |
| M   | 55  | AMS                                                                     | bifocal                                                               | Sequalae                     |
| M   | 65  | Lt H                                                                    | Rt parietal                                                           | Sequalae                     |
| F   | 48  | AMS                                                                     |Lt cerebellar                                                          | Full Recovery                |
| F   | 49  | AMS, hypotonia                                                          | bilateral cerebellar, occipital                                        | Sequalae                     |
| F   | 48  | AMS                                                                     | Rt cerebellar, medulla, pons                                           | Death [7]                    |
| M   | 43  | Lt H, AMS                                                               | Rt MCA                                                                | Sequalae                     |
| F   | 24  | Lt H, right homonymous hemianopsia                                       |Lt MCA with ICH                                                        | Sequalae                     |
| M   | 62  | Rt H                                                                    |Lt MCA                                                                 | Sequalae                     |
| F   | 32  | AMS, O                                                                  |                                                                          |                              |
| M   | 18  | Aphasia, Rt H                                                           |Lt MCA                                                                 | Sequalae                     |
| M   | 24  | coma, akinetic mute                                                     | bilateral ACA                                                         | Sequalae                     |
| F   | 56  | P, O                                                                    | Cerebellum, bilateral frontal, parietal                               | Full Recovery                |
| M   | 37  | P, O, Lt H                                                              |                                                                         |                              |
| F   | 45  | P, O, Lt H                                                              |                                                                         |                              |
| Author | Year | Gender | Age | GCS | LOC | Injury | Outcome |
|--------|------|--------|-----|-----|-----|--------|---------|
| Al-Sadawi et al. | 2019 | Male | 53 | 14 | 6 | P.O | Death [5] |
| Prakash, 2008 | | Male | 40 | 3 | 8 | P.O, Locked in syndrome | Full Recovery |
| Mugundhan, 2008 | | Male | 14 | 8 | 7 | P.O, Locked in syndrome | Full Recovery |
| Santos-Soares, 2007 | | Male | 65 | 8 | 5 | Aphasia, Rt H, Lt facial palsy | Full Recovery |
| Das, 2007 | | Male | 22 | 15 | 10 | Aphasia, Rt H | Sequalae |
| Thomas, 2007 | | Male | 46 | 15 | 12 | Lt inferior quadrantanopsia | Full Recovery |
| Merle, 2005 | | Male | 66 | 13 | 8 | Lt H, left homonymous hemianopsia | Sequalae |
| Anim, 2004 | | Male | 22 | 15 | 10 | decreased visual acuity | Sequalae |
| Loe, 2004 | | Male | 52 | 13 | 5 | Lt H, Rt facial palsy, Lt H | Sequalae |
| Barholdi, 2004 | | Female | 32 | 15 | 10 | Lt H, Rt Facial palsy, Wernicke’s aphasia | Sequalae |
| Boviatsis, 2003 | | Female | 22 | 15 | 10 | Lt H, Rthemianopsia | Full Recovery |
| Zhang, 2003 | | Male | 46 | 15 | 12 | Lt H, aphasia | Sequalae |
| Hung, 2003 | | Male | 57 | 11 | 7 | coma, anisocoria | Sequalae |
| Dinh, 2001 | | Male | 64 | 15 | 10 | coma, anisocoria | Sequalae |
| Loe, 2001 | | Male | 65 | 13 | 5 | Lt H, one and-a-half syndrome | Sequalae |
| Panicker, 2000 | | Male | 23 | 15 | 10 | Motor aphasia, Rt H | Sequalae |
| Singh, 1998 | | Male | 57 | 13 | 5 | coma | Full Recovery |
| Cole, 1996 | | Male | 43 | 14 | 5 | Wernicke aphasia, alexia, quadrantanopsia, Rt H | Sequalae |

GCS: Glasgow Coma Scale, CT: Computed Topography, MRI: Magnetic Resonance Imaging, M: Male, F: Female, Lt: Left, Rt: Right, H: Hemiplegia, O: Ophthalmoplegia, P: Ptosis, AMS: Altered Mental Status, ICH: Intra-Cranial Hemorrhage, MCA: Middle Cerebral Artery, ACA: Anterior Cerebral Artery, ICA: Internal Carotid Artery, PICA: Posterior Inferior Cerebral Artery