

Neurotoxic Manifestation of Snake Bite in Bangladesh

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Abstract

Introduction: Snake bite is a potentially life threatening emergency situation physician has to encounter in rural areas of tropical countries in South-East Asia including Bangladesh. Among the venomous snakes in Bangladesh, Neurotoxic snakes like Cobra and Krait are the commonest. In this study neurotoxic manifestation of venomous snakes are clinically observed.

Methods: In this series a total 35 snakebite patients with neurological features from May 1999 to June 2001 were included and preexisting neurological cases were excluded.

Results: Among the 537 total snake bite cases, the neurotoxic snake bite was 10% with 51 cobra bite and 12 kraits bite. The victims age are in the range of 3.5 years to 85 years with 70% cases are under 30 years of old. There is slight male preponderance with almost same number of bite at home and outside. The common clinical neurotoxic features are ptosis, (100%) external ophthalmoplegia, dysphagia, dysphonia and broken neck sign. The chest movements were reduced in 20 % cases. All 35 cases (100%) were treated with Haffkine polyvalent anti snake venom with 8.6% cases needed 2nd dose. All 35 cases with neurotoxic features were also treated with anti cholinesterases (100%) and among them 14.2% needed ventilatory support. Anti-snake venom reaction was very common in the with pyrogenic reaction (80.64%) and anaphylactic reaction (64.51%). The outcome of snake bite was excellent with 97% recovery with one residual neurological deficit and no fatality.

Conclusion: The neurotoxic snake bite has definite characteristics neurological sign and symptoms which could lead to fatality with respiratory paralysis.

Keywords: Neurotoxic; Venomous; Snake

Introduction

Snake bite is a potentially life threatening and important emergency situation a physician has to encounter in rural areas of tropical countries in South-East Asia including Bangladesh (Warrell, 1995). The importance of snake bite has been emphasized by the WHO [1]. In a recent study conducted in 1995-1996 it has been shown that incidence of snake bite is 4.3 per 100,000 populations with mortality of 20%. Epidemiological aspects of snake bite and clinical presentation following bite has been described from different countries. Several measures were taken to characterize the venoms and standardize the antivenoms [2-4].

There are about 82 species of snakes in Bangladesh amongst which 28 species are venomous and others are non-venomous. The venomous snakes of medical importance in our country is *Cobra*, *Naja*, *Gokhra*; *Krait*, *Bangarus*, *Shakhini*, *Kewtey*; *Russells Viper*, *Doboia russelii*, *Chandrorora*; *Green snakes*, *Trimeresurus*, *Gal tawa*;

King cobra, *Ophiophagus*, *Shankachur* or *Khalandar*, and all species of sea snakes. Medically important snake species are the ones that fill into one of the three categories: a) commonly cause death or serious disability, b) uncommonly cause bites but are recorded to cause serious effects, c) commonly because bites but serious effects are very uncommon [1].

Effects of snake bite involve different systems depending upon species of snakes causing bite [5]. Cobra and Krait bites are associated with prominent neurotoxicity. Local envenoming with soft tissue necrosis has also been described in some countries including Bangladesh following Cobra bite [6,7] but the krait bite is not associated with any local envenomation. Russell's viper bite is associated with coagulation abnormalities and renal failure with occasional reports of neurotoxicity, pituitary necrosis and increased vascular permeability [8]. Green snake bite is associated with swelling of the bitten part and coagulation abnormality. The sea snake bite is associated with neurotoxicity, myotoxicity and renal failure. The common serious envenoming is neurotoxicity which is characterized

by ptosis, external opthalmoplegia, dysphagia, dysphonia, weakness of facial muscles, broken neck sign (weakness of neck muscles leading to unable to flex the neck), loss of tendon jerks and respiratory paralysis [9]. Considerable geographical variation in clinical presentation has been described following bite by some species of snakes including Cobra and Russell's viper [10]. Diagnosis of species of snake responsible for bite is essential for management of patients. Estimation of venom antigen from swab from wound site, serum or urine by Enzyme Linked Immunosorbent Assay (ELISA) technique has been found to be useful in some countries [11]. In absence of such facilities, good epidemiological study by identification of brought dead snake may be helpful in correlating clinical features with type of snakes. Careful documentation of clinical features following bite by different snakes is needed in Bangladesh. Most often people seek treatment from traditional healers called 'ozha'. As a result doctors in the community are not appropriately aware of various aspects of snake bite and its management. Venomous snake bite with neurotoxic features consist the major venomous bite in our country. Unfortunately many of the published cases of neurotoxic snake bite are poor to describe due to lack of detailed examination and observation. An attempt has been made in this study to describe clinical presentation of patients of snake bite presented with neurological features. Species identification of the offending snake was also attempted to define the snake in our country which causes neurotoxicities after venomous bite.

Materials and Methods

In this series a total 35 snakebite patients with pure neurological features were included. All patients having one or other neurological manifestation with or without local envenomation after snake bite were admitted and treated in snake bite study clinic (SBSC) under medicine unit-III in Chittagong Medical College Hospital. (Only unit where all the patients of snake bite is admitted in C.M.C.H.). This study was carried out over the period of 2 years ranging from May 1999 to June, 2001.

Any patient, who presented with one or more of the recognized neurotoxic features developed after snakebite of all ages and both sexes, was included in this study. However, patients having history of pre-existing neurological disease were excluded from the study. Venomous snake bite leading to cardiotoxicity, renal failure or coagulopathy was also excluded from the study. The patients who received antihistamine, sedative or steroids in pre hospital or primary care management were also not included in this study.

A detailed history was taken from each of the patient and/or attendant and relevant points for example: time and place of bite, sequence of occurrence of symptoms with progression, pre-hospital treatment history etc. was specially sought. Simultaneously thorough physical examination especially detailed neurological examination was done. Local examination was also done minutely to note fang marks, swelling, tenderness, blistering, enlarged and tender lymph nodes etc.

Special inquiry was done to identify the offending snake by asking the party to bring the snake (if it had been killed) for direct identification. The identification of snakes that were not brought to hospital was done by showing photographs or preserved samples.

Some investigations were done to search probable complications like excessive muscle breakdown, cardiotoxicity, coagulation abnormality etc. Investigations carried out routinely include Haemoglobin level, TC and DC of WBC, serum CPK, ECG and 20

min whole blood clotting test (20 min WBCT). Bed side peak expiratory flow rate (PEFR) was done in every patients except those presented with ventilatory failure or unconscious. All patients were observed for 5 days in hospital to see recovery, anti-snake venom reaction and any early residual neurological deficit present or not. If the patients developed neurological deficit or local envenomation, further observation by neurologist and surgical specialist was done.

All enrolled patients with features of neurotoxicity (one or more) were treated with polyvalent anti-venom and in Neostigmine. In some cases artificial ventilation were given for variable durations. The outcome of treatment was noted in all cases. The collected data is preserved and analysis done with EP Info 6 manual and expressing results in percentage and number.

Results

During the study period (May 1999 to June 2001) a total 537 snake bite patients were admitted. 365 patients were non venomous and 172 patients were venomous bite patients. Green pit bites (102 pt) were highest among the venomous patient. 63 patients (cobra-51 and krait-12) presented with neurotoxicity with or without local envenoming. The other venomous bite patients were sea snake (05) and Russell's viper bite (02). Among the venomous bites, 35 patients presented with neurological manifestations with or without local necrosis were included in the study. The other 28 neurotoxic patients were excluded due to presence of prior neurological disease, prior treatment with antihistamine, sedative or steroids in prehospital or primary health care.

Age: The age of the studied patients ranged from 3.5 to 85 years. Most of the victims were between 5 to 30 years that comprised 70% of total patients (Table 1).

Age (years)	Number of patient	Percentage
1-5	1	2.85
6-10	6	17.14
11-20	11	31.42
21-30	8	22.85
31-40	4	11.42
41-50	2	5.71
>50	3	8.57

Table 1: Age distribution (n=35) of neurotoxic snake bite.

Sex: Among the patients, males were a bit predominant (54.2%).

Pre-hospital treatment: All patients received some types of treatment before coming to the hospital. Most of those treatments were traditional and harmful. All patients received multiple tight tourniquets over the bitten limb, some of which were tight enough to cause arterial occlusion. Others include suction of bitten site, application of stone/seeds, multiple incisions over bite vicinity, attempt of induced vomiting, recitation by 'ozha' (Table 2).

Example	Number of patient	percentage
Application of multiple ligature	35	100
Immobilization	0	0
Suction of bitten limb	7	20
Application of stone/seed	6	17.14
Incision at bite vicinity	10	28.57
Attempt of induced vomiting	6	17.14
Recitation by Ozha	17	48.57

Table 2: Pre-hospital treatment (n =35).

Clinical features

Neurological manifestations

Most common neurological manifestation observed was ptosis of varying degrees, which was present in all patients (Table 3).

Features	Number of patient	Percentage
Ptosis	35	100
External ophthalmoplegia	33	94.2
Broken neck sign	28	80
Dysphagia	27	77.1
Dysphonia/nasal voice	24	68.5
Weakness of grip	23	65.7
Depressed reflexes	9	25.7

Table 3: Neurological features (n=35).

The next common was external ophthalmoplegia. Others were broken neck sign (weakness of neck muscles), dysphonia particularly nasal voice, dysphagia, weakness of grip, inability to open mouth, depressed reflexes, generalized weakness. Patients presented in primary care hospital with sign and symptoms of neurotoxicity and referred with documentation were also entered in the data process. Three patients presented with unconsciousness in SBSC were seen in primary health care with ptosis, ophthalmoplegia, dysphonia, dysphagia etc and were referred early for management. All patients had some amount of weakness of limb muscles.

Chest movement

Chest movement was diminished in 7 patients of whom five patients developed complete respiratory paralysis and needed artificial ventilator support.

Features of local bite area

On local examination, typical double fang marks were found in 20 patients and single fang mark in the 13 patients. The affected area was tender in all cases, hot in 23 cases (65.71%) and the limb was swollen in 26 (74.28%). In 18 cases enlarge and tender local lymph nodes were palpable (Figure 1).

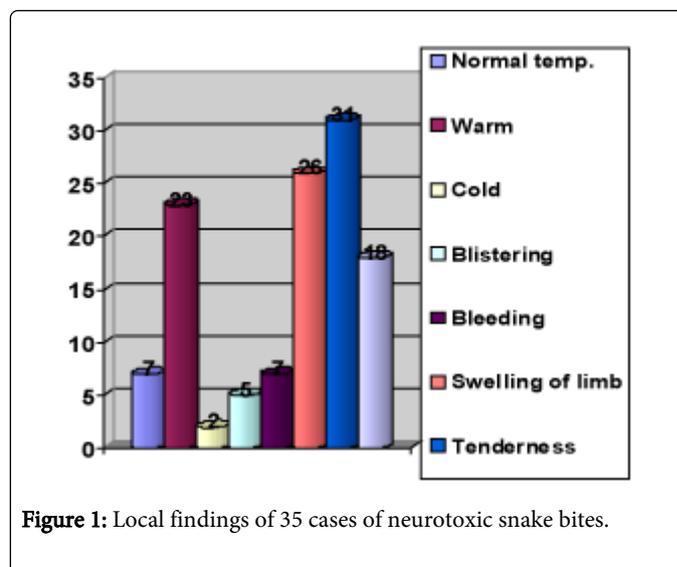


Figure 1: Local findings of 35 cases of neurotoxic snake bites.

Investigations

Regarding investigations 23 patients had neutrophil leukocytosis (Table 4).

Investigation	Number of patient	Percentage
Polymorph leukocytosis	23	65.7
Urinary albumin	19	54.2
Abnormal ECG	2	5.7
20 min. WBCT abnormal	35	0

Table 4: Investigations findings (n=35) of Neurotoxic snakebite cases.

Urinary albumin was found in 54% cases. Bedside 20-min. whole blood clotting test was normal in all cases indicating no coagulation abnormality. ECG was abnormal only in two patients.

Identification of snakes

The offending snakes were identified in 15 cases; the snake was Monocellate Cobra (*Naja kaouthia*) in all those cases. Nine patients could bring the snake and six patients could identify the offending snake by seeing the photograph of Cobra. The identification process of brought snake, photograph or preserved specimen did not identify the other 20 snakes. The victims saw snakes in brief period in those cases and it could be either cobra or krait.

Treatment

All enrolled patients were treated with polyvalent antivenom. The criteria for antivenom administration were one or more neurological manifestations. Single doses (10 vials) in saline solution were given initially to all patients and 3 patients needed 2nd dose of antivenom due to lack of response.

Auxiliary treatment

Along with anti-snake venom the anticholinesterase Neostigmine was given to all patients. Five patients required artificial ventilation for variable duration.

Anti-venom reaction (Type)

31 cases developed one or many anaphylactic reactions. Among them 20 patient developed early anaphylactic reactions, 25 patient developed pyrogenic reaction and 14 patient developed both anaphylactic and pyrogenic reaction.

Anaphylactic reaction

In these series 20 patients out of 35 developed anaphylactic reaction in different ways. Most cases (16 patients) presented with urticaria with itching. The next common presentation was nausea and vomiting (8 patient). The same number of patient (8) was also have vigorous presentation with bronchospasm which was clinically presented with wheeze, rhonchi, crepitation etc. Only 2 patient developed angioedema in this series. The other uncommon presentation was with cough (3 pt), headache (2 pt), fever (3pt), tachycardia and palpitation (2 pt).

Time of recovery

After anti-venom therapy, time required to recover from neurological manifestations ranged from 0.5 hour to 48 hours with a median of 4 hours (Figure 2).

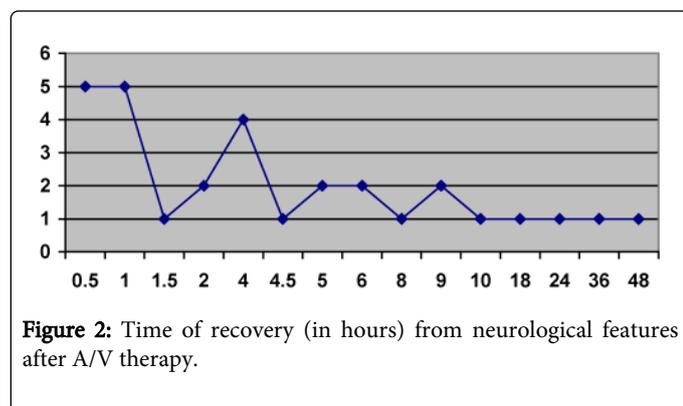


Figure 2: Time of recovery (in hours) from neurological features after A/V therapy.

Outcome of treatment

In this series 34 cases of neurological manifestation were completely recovered. There was a single case with persistent neurological sequelae. There was no death in this study group of patient.

Discussion

The age of the patients range from 3.5 years to 85 years. Most of the victims were between 5-30 years of age comprised (70%). It indicates that, growing and active parts of the society are bitten by the snakes [12,13]. Males are higher than the females as they are in special risk of out-side activity especially during cultivating and harvesting seasons. Thus this is an occupational hazard of young and active males especially those who work in hilly area and forest [12,13].

All the patients bitten by snakes with neurotoxic envenomation in our study showed a similar pattern of neurological manifestations. Two outstanding and severe clinical effects were noted in the present

series. First was neuromuscular curare like effects, esp. the effect on respiratory muscles which frequently led to breathing failure and second was its necrotic effect on skin and subcutaneous tissue around the bite site, which in many cases resulted in wide slough lesions.

When the time of onset of the paralysis (Blurring vision, double vision, difficulty in swallowing or opening mouth etc all indicate commencement of muscle paralysis) could be reasonably determined (35 patients) the average time between the bite and the development of symptoms attributable to the paralysis was 4 ½ hours, with a range 1 to 10 hours. The overt neuroparalysis with many features developed 45 min to 10 hours after the first symptom of envenomation, indicating that there was a significant latent period between the first evidence of the absorption of venom and the development of paralysis. This study is consistent with the study of study in Thailand [14] where the interval was 8 hours and Campbell, C. H in which the interval was 5 ½ hours [15]. So it can be said that the envenoming process takes time to develop (hours) and there is a latent period between interaction with snake and gross neuroparalysis.

The first sign of neurotoxicity is ptosis (incomplete or complete) with external ophthalmoplegia in most cases in this study (100% for ptosis and 94.2% for ophthalmoplegia) showed that the paralysis always appears first in the muscles supplied by the cranial nerves, usually in the external ocular muscles or the muscles which elevate the upper eye lids. This observation is also consistent with the study in Thailand by Mitrakul C. where ptosis predominantly presented in 63% of cases [14] and study in Papua by Campbell CH [15]. The next common sign observed in this series was dysphagia 27 patients (77.1%) and dysphonia 24 patients (68.5%), which indicate the relatively early involvement of muscles of tongue, palate, pharynx and jaw rather than limbs or chest muscles [16]. The pooling of secretion and inability to open or close the mouth is frequently observed in this series, which also dictates the statement to be a correct one. 28 patients in this series showed broken neck sign (80%), which was associated with weak neck flexion in most of the patients. Weakness of grip was seen in 23 of the cases (65.7%) and loss or depressed of deep reflex was seen in only 9 cases (25.7%). The huge involvement of neck muscle explained the traditional belief of sequential muscle paralysis is not true rather several muscles group are frequently involved together [15,17]. In the clinico-epidemiological study done by Faiz et al. in 1999 in CMCH, the neurological manifestations among the venomous bites were similar to this study. Diminished chest movement were present in 7 cases out of whom 5 patients (14.2%) developed severe respiratory paralysis requiring artificial ventilatory support for variable duration (Ranged from 1hour to 48 hours with a median of 15 hours). In this group, two patients (both female of middle age) presented with apnoea as well as imperceptible pulse and blood pressure. Sensory function was intact in all cases except three, who were unconscious at presentation as well. Consciousness level was all right in rest of the cases even when they were under ventilator. It suggests that the neurotoxic venom acts mainly on peripheral nervous system [17].

In this study, commonest (70%) abnormal laboratory result during first few days after bite was mild to moderate leukocytosis with neutrophilia. Raised serum CPK was found in 50% cases with most of them had tight tourniquet for long duration suggesting muscle damage by pressure effect. ECG was abnormal in 5 cases. One female middle-aged patient had fast atrial fibrillation, which persisted later. This AF might have present from beforehand. Another female patient of 50 years had some ECG features of hypokalaemia. It was confirmed by doing serum electrolyte levels where serum potassium was 3.3

mmol/L. This may be due to imbalance in I/V fluid infusion. In other 3 cases there were features of partial Right Bundle Branch Block. The normal 20 min. whole blood clotting test in all cases confirmed that there was no clotting disturbance, which is consistent with Elapid bites of our country.

Identification of an offending snake is not very easy, because the incident is very sudden and mostly accidental and in most cases happens in dark bushy areas or at night. In spite of above facts, in this study offending snake was identified in 15 cases (42%), all were Monocellate Cobra (*Naja kauthia*). In nine cases the party brought the snake along with them-7 dead and 2 alive. Other 6 patients described the snake specifically and identified the snakes by seeing photographs. All these 15 cases of definitive cobra bite also had features of local envenoming (pain, swelling, and necrosis) along with neurotoxicity. Among the unidentified cases, twelve patients had exactly similar features; thus they would be cobra bite as well. Remaining 8 cases had no/minimal features of local envenomation and possibly they could be due to krait bite. Thus it can be simply said that most common venomous snake with neurological manifestations in this region is monocellate cobra, *Naja kauthia*.

All patients of this study were treated with Haffkine's polyvalent anti-venom. This anti-venom is effective against envenomation by Cobra, Krait, Russell's viper and Saw-scaled viper. A single dose of A/V consists of 10 vials (each-10 mg). Most of the patients respond to single dosage of A/V. In 3 cases, second dose was needed as they did not show any improvement (even deterioration occurred) after 2-3 hours of first dose. Definitive improvement was observed after 2nd dose. Only one patient who required two doses of A/V that were given at 3-4 hours interval had neurological sequelae. The number of doses required was not proportionate to the time between bite and hospitalization. Two patients required two doses even they were admitted within 2-3 hours of bite. On the other hand, one patient, who was admitted 23 hours after the bite, responded very well to single dose. May be the amount of injected during bites and reversibility of binding of venom with neuromuscular junction play the main role. All patients of this study also received anticholinesterase-Neostigmine for variable duration depending upon the severity of neurotoxicity. This was proved to be very much effective [18,19] especially when there was impending respiratory failure as evident by diminished chest movement.

Respiratory failure, the most ominous sign (present in 5 pts) in this study was consistently heralded by other milder neuromuscular changes. Nonetheless, in many cases apnea had quite an early onset, as early as 2.5 hours after the bite. This was also observed by Mitrakul et al. [14]. Victims of cobra bite or suspected victims should therefore be observed closely for neurological signs immediately after the bite and for at least 24 hours, regardless of the severity of the early local changes. Mechanical ventilation was required in 5 patients; the duration ranged from 1 hour to 48 hours. All these patients could die of snakebite without the facility of artificial ventilation. Therefore, facilities for endotracheal intubation and artificial ventilation are mandatory for total and comprehensive management of neurotoxic snake bite.

As the anti-venom that was used was horse serum, A/V reaction was very common. But all reactions could be managed easily with recommended regimen as requires [19]. It indicates that, frequent A/V reactions should not be taken as frightening thing and A/V therapy must be given in all cases where indicated.

All patients survived after effective management. Complete recovery was observed in 34 cases, the recovery time (from neurotoxicity) ranging from 0.5 hour to 48 hour with a median of 4 hours. Only one patient recovered after getting 2 doses of A/V with some distinctive neurological sequel in the form of generalized tonic-clonic seizure, myoclonus, cerebellar and extrapyramidal features. These features persisted months after his discharge (till last follow-up). CT scan and MRI of brain were done but no definitive lesion could be detected. Consultation was done with expertise and it was inferred that these sequel are due to hypoxic brain damage, which occurred during the brief period of apnea before starting mechanical ventilation.

Conclusion

Although most of the snake bite is nonvenomous, it is important to differentiate it from venomous snake bite that needs immediate attention and specific management. The venomous snake bite may present with local or systemic envenoming in the form of neurotoxicity, vasculotoxicity, myotoxicity, cardiotoxicity etc. The neurotoxic snake bite with respiratory paralysis is the prime cause of death in venomous bite in Bangladesh.

The Elapidae group of snakes are (especially cobra and krait) the neurotoxic with or without local envenoming in our country. The neurotoxic features are ptosis, external ophthalmoplegia, broken neck sign, dysphagia, dysphonia, weakness, depressed reflex which can lead to fatal respiratory paralysis. Although the identification of snake is sometimes troublesome there is 'Syndromic Approach' to ameliorating the problem. Handling the snake is dangerous but it is wise and helpful for management if the dead specimen is brought to the health facility.

The diagnosis is straightforward if there is gross neurotoxicity and the specimen is brought in front. Although laboratory investigation is nonspecific, ELISA method to detect and analysis the venom components is matter of huge interest to medical scientist. Venom antigenemia, electrophysiology, histopathology, genetics etc all are currently involved in diagnosis and management of snake bite.

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Conflict of Interest

There is no conflict of interest in design, conduction and publication of the study.

Ethical Approval

The study received approval from the Ethical Review Committee of the CMCH. From all patients informed written or verbal consent was taken.

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