Neurological Manifestations of Snake Bite in Sri Lanka
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Abstract:
BACKGROUND AND AIMS: Snake bite is an important cause of mortality and morbidity in certain parts of Sri Lanka. This study was designed to determine the offending snakes, neurological manifestations, disease course, and outcome in neurotoxic envenomation. METHODS AND MATERIAL: Fifty six consecutive patients admitted with neurological manifestations following snake bite were studied prospectively. Data were obtained regarding the offending snakes, neurological symptoms, time taken for onset of symptoms, neurological signs, and time taken for recovery. RESULTS: The offending snake was Russell’s viper in 27(48.2%), common and Sri Lankan krait in 19(33.9%), cobra in 3(5.4%), and unidentified in 7(12.5%). Ptosis was the commonest neurological manifestation seen in 48(85.7%) followed by ophthalmoplegia (75%), limb weakness (26.8%), respiratory failure (17.9%), palatal weakness (10.7%), neck muscle weakness (7.1%), and delayed sensory neuropathy (1.8%). Neurological symptoms were experienced usually within 6 hours after the bite. Following administration of antivenom, the signs of recovery became evident within a few hours to several days. The duration for complete recovery ranged from four hours to two weeks. CONCLUSIONS: Complete recovery of neuromuscular weakness was observed in all patients except for one who died with intracerebral haemorrhage shortly after admission. (J Postgrad Med 2002;48:275-279)

Key Words: Snake bite; neurotoxic envenomation; antivenom

Snakebite is an important health problem in Sri Lanka, particularly in rural and farming areas. In 1999, there were 32,303 cases of snakebite with a case fatality rate of 0.6%. In the country, approximately 95% of the mortality is attributable to bites by the cobra (Naja naja), Russell’s viper (Daboia russelii), common krait (Bungarus caeruleus), and Sri Lankan krait (Bungarus ceylonicus).

The principal effects of envenomation with snake toxins are related to neurotoxicity, nephrotoxicity, myotoxicity, cardiotoxicity, coagulopathy, vascular endothelial damage and local reactions. Muscle weakness following snake bite has been reported by several authors. Clinical and electrophysiological studies have demonstrated defective neuromuscular transmission as a causative mechanism. However, there have also been reports of muscular weakness due to rhabdomyolysis. This study was designed to define the snakes causing neurotoxicity, spectrum of neurological manifestations following envenomation, disease course and outcome.

Patients and Methods
This study was conducted at the Base Hospital of Polonnaruwa, which is situated in the dry zone of Sri Lanka in the north-central province, about 200 kilometers away from the capital city of Colombo. The majority of the population is engaged in farming and snakebite is a major occupational hazard particularly during the harvesting season. We prospectively studied all patients admitted with neurological manifestations due to snakebite. The study was carried out over an eight-month-period beginning July 2000. The offending snake was identified either by direct examination (when the snake was killed and brought to the hospital) or on the basis of eye-witness account. This evidence was further verified by showing photographs of snakes to the eye witness.

Details of history were obtained and patients were subjected to neurological examination soon after admission. They were regularly assessed hourly for the first six hours, 12 hourly for next 72 hours, and then daily until complete recovery. Information regarding progression, onset of recovery and results of biochemical investigations were entered in a pre-designed performa. Some patients underwent intravenous edrophonium test, whose results were also noted.

The patients were treated with lyophilised polyvalent enzyme refined equine immunoglobulins (antivenom serum; Hafighe Institute, Mumbai, India) produced against Naja naja, Bungarus caeruleus, Vipera russelii, and Echis carinatus. Based on previous evidence, a single dose of 10 ampoules, each reconstituted with 10 ml of diluent, and further diluted in 500 ml of isotonic saline was infused intravenously over one hour. Those who elicited a positive response to Tension test were treated with oral neostigmine until complete neurological recovery.
Results
Fifty-six patients (45 males, 80.4%) in the age range of 13-65 years (Mean age 31.9±12.1) were enrolled. The snake could be identified in 49 of them by virtue of direct examination in 20 and on the basis of eye-witness accounts in another 29. Russell’s viper bites (48.2%) were most commonly reported. Common krait and Srilankan krait were responsible in 19 (33.9%) while cobra was responsible for 3 (5.4%) cases. The offending snake could not be identified in seven (12.5%).

Nine patients (16.1%) developed neurological symptoms within 30 minutes of the bite whereas 26 (46.4%) reported symptoms from 30 minutes to two hours after the bite. The onset of symptoms was from two to four hours after the bite in 13 (23.2%). In a minority (8 cases; 14.2%) symptoms occurred after four to six hours. The most common symptom was drooping of eyelids followed by double vision and dysphagia (Table 1).

We analysed different neurological manifestations with time taken for onset of recovery and complete recovery in each case (Table 2). Ptosis was the commonest sign seen in 48 (85.7%) cases. The evidence of recovery was seen as early as two hours after the infusion of antivenom in ten patients. The longest time taken for onset of recovery was seven days. Complete recovery was noted within ten hours in nine patients while the longest duration reported was two weeks. Ten patients developed respiratory muscle weakness necessitating mechanical ventilation. The majority of them (8) were bitten by the krait. There was one victim of Russell’s viper bite and the offending snake was not identified in the other. No patient with neuromuscular weakness had permanent sequelae.

There was only one death in the series. It was a 40-year-old male admitted with bleeding manifestations, bilateral ptosis, limb weakness and Glasgow Coma Scale of 3/15 following a Russell’s viper bite. He died within three hours of admission despite transfusion of blood, plasma, and antivenom. The autopsy revealed a large intracerebral haemorrhage in the right parietal region.

One patient developed peripheral sensory neuropathy two weeks after a krait bite. He was admitted with limb weakness along with respiratory failure and was mechanically ventilated for ten days. Four days after weaning off of the ventilatory support, he developed numbness in all the extremities, which reached the peak disability in one week. Neurological examination revealed normal muscle power, hyporeflexia, and ‘glove and stocking’ type peripheral sensory loss for pain and touch. On electrophysiological evaluation, the motor nerve conduction studies were normal. Sensory conduction velocities in median and ulnar nerves were slower with reduced amplitudes. Sensory nerve action potentials of sural nerves were absent while cerebrospinal fluid analysis was normal. His symptoms showed amelioration when the patient was seen at follow-up visit one month later.

Edrophonium test (10 mg intravenous dose) was performed in 8 patients. The rest could not be tested due to unavailability of the drug. Seven showed a positive response in whom the offending snakes were krait in three, Russell’s viper in two, and unidentified in two. All seven patients had ptosis whilst six had external ophthalmoplegia, in addition. Neck muscle weakness and dysphagia were found in four patients each. Weakness of limb and jaw muscles was detected in three and one cases respectively. One patient developed ventilatory failure due to respiratory muscle weakness necessitating mechanical ventilation. Following edrophonium injection, improvement in ptosis was seen in one, ptosis with limb muscle weakness in one, and limb muscle weakness alone in one. The snake was

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of patients</th>
<th>Table 1: Neurological Symptoms Reported by the Patients with Snake-bite</th>
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<tbody>
<tr>
<td>Drooping of eye lids</td>
<td>48 (85.7)</td>
<td></td>
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<tr>
<td>Double vision</td>
<td>46 (82.1)</td>
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<tr>
<td>Dysphagia</td>
<td>18 (32.1)</td>
<td></td>
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<tr>
<td>Breathing difficulty</td>
<td>18 (32.1)</td>
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<tr>
<td>Limb weakness</td>
<td>15 (26.8)</td>
<td></td>
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<tr>
<td>Jaw weakness</td>
<td>13 (23.2)</td>
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<tr>
<td>Slurring of speech</td>
<td>11 (19.6)</td>
<td></td>
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<tr>
<td>Blurring of vision</td>
<td>6 (10.7)</td>
<td></td>
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<tr>
<td>Neck weakness</td>
<td>4 (7.1)</td>
<td></td>
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<tr>
<td>Nasal regurgitation</td>
<td>2 (3.6)</td>
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</tr>
</tbody>
</table>

Figures in parentheses indicate percentages.

<table>
<thead>
<tr>
<th>Sign</th>
<th>Number</th>
<th>Time for onset of recovery</th>
<th>Time for complete recovery</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>Mean</td>
</tr>
<tr>
<td>Ptosis</td>
<td>48 (85.7)</td>
<td>2 hr-4 d</td>
<td>39.5 hr</td>
</tr>
<tr>
<td>Ophthalmoplegia</td>
<td>42 (75)</td>
<td>2 hr-4 d</td>
<td>39.8 hr</td>
</tr>
<tr>
<td>Limb weakness</td>
<td>15 (26.8)</td>
<td>2 hr-4 d</td>
<td>36.5 hr</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>10 (17.9)</td>
<td>12 hr-7 d</td>
<td>2.2 d</td>
</tr>
<tr>
<td>Palatal weakness</td>
<td>6 (10.7)</td>
<td>2 hr-7 d</td>
<td>2.2 d</td>
</tr>
<tr>
<td>Neck muscle weakness</td>
<td>4 (7.1)</td>
<td>2 hr-4 d</td>
<td>2.5 d</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate percentages. d: days; hr: hours
unidentified in the victim with a negative edrophonium response. Those who showed positive response to edrophonium test were started on oral neostigmine along with antivenom therapy. Complete recovery of neurological manifestations was observed within five days in four cases. Two patients took eight days for full recovery. The patient who developed ventilatory failure needed two weeks to recover completely.

**Discussion**

Proteins such as enzymes, non-enzymatic polypeptide toxins, and non-toxic proteins are major components of snake venom. Neurotoxins bind to neuromuscular junction both pre- and post-synaptically causing muscle weakness. Alpha-bungarotoxin of krait binds to acetylcholine receptors and is used experimentally to demonstrate reduction in acetylcholine receptor sites in postsynaptic membrane. Alpha-cobra toxin which has a similar action produces features of myasthenia gravis in the experimental animals. Phospholipase A2 enzyme and Beta-bungarotoxin act pre-synaptically to cause neurotoxicity.

Neurotoxins of snake venom seem to affect various sites of neuromuscular system. Myotoxic effects causing rhabdomyolysis has been reported. Clinical and electromyographic evidence of myokymia have been demonstrated in victims of timber rattlesnake bite (Crotalus horridus horridus) suggesting increased peripheral nerve terminal excitability. There is substantial clinical and electrophysiological evidence of defective neuromuscular transmission, both pre-synaptic as well as post-synaptic, in neurotoxic envenomation. Singh et al based on the electrophysiological assessment in patients with Bungarus caeruleus bite postulated that both pre-synaptic and postsynaptic blockade at neuromuscular junction are responsible for the neuromuscular manifestations.

Another study of three cases of envenomation by Papuan taipan snake (Oxyuranus scutellatus canni) demonstrated reduced compound muscle action potentials (CMAP), post-activation potentiation and decremental response on repetitive nerve stimulation (RNS) at 5 Hz, and increased jitter with blocking on single fibre EMG suggesting pre-synaptic blockade. In two patients with envenomation by Philippine cobra (Naja naja philippinensis), Watt et al showed decremental response to RNS at 5 Hz with reversal of it after administration of intravenous edrophonium indicating post-synaptic blockade. A study from Sri Lanka showed normal nerve conduction studies, normal EMG, and decremental response to RNS at 20 Hz and 50 Hz. All these studies provide good evidence of defective transmission at neuromuscular junction in victims of snake bite. The positive response to Tensilon test also supports this hypothesis. A previous study has shown significant improvement in muscle weakness after administration of intravenous edrophonium in neurotoxic envenomation by the Philippine cobra. The treatment of patients with neurotoxic envenomation with anticholinesterases is debatable as some studies show favourable results, while others do not. However, neurophysiological abnormalities seem to correlate well with clinical findings. It is of interest to note that in the current study, six out of seven patients with positive response to edrophonium test, who were treated with oral neostigmine made full recovery within eight days. However these numbers are too small to draw any conclusions with regard to efficacy of anticholinesterases. In the light of above findings, even though the data are not sufficient enough to make an unequivocal decision, it would perhaps be reasonable to offer anticholinesterase therapy for those who demonstrate positive response to Tensilon test or decremental response to RNS.

Respiratory muscle weakness is a potentially fatal manifestation of snake bite. Krait bite is especially notorious for rapid development of respiratory failure. However, in our series all ten patients with respiratory failure were successfully managed with the help of mechanical ventilation. This emphasises the importance of anticipation of this complication and timely intervention.

There are reports of Guillain-Barre syndrome following snake bite. One patient in our series who suffered a krait bite developed peripheral sensory neuropathy. He had no other demonstrable cause such as herbal treatment, alcohol intake or vitamin deficiency to account for the neuropathy. The clinical and neurophysiological findings were not compatible with critical illness neuropathy. It could be postulated that either direct neurotoxicity or a reaction to antivenom may have been responsible for these manifestations. Adverse reactions to antivenom appear in two forms; early and late. Early reactions tend to occur within 10 to 180 minutes after treatment and range from urticaria to anaphylactic shock. Late reactions are immune complex diseases and present in the form of serum sickness syndrome usually 5 to 24 days after antivenom administration. Both central and peripheral nervous system manifestations are seen in association with serum sickness. In view of delayed onset, some form of immune-mediated neuropathy is perhaps more likely in our
patient. However, the available data is insufficient to draw any conclusions regarding exact aetiology. Autoantibody assays such as anti ganglioside antibodies, immune complex studies, serial electrophysiology and nerve biopsy would be useful to elucidate the mechanism of delayed neuropathy following neurotoxic envenomation.

It should be noted that in 29 cases the snake was identified on the basis of eye-witness accounts. We have not made an attempt to strictly correlate all clinical findings with snake species as the above method of identification may not be absolutely foolproof, even though inhabitants of the area are very familiar with snakes.

References

result of depletion of clotting factors. Ischaemic stroke following snakebite is rare but is reported with viper bite.7,9 Most viper venoms exhibit both coagulant and anti-coagulant properties, and contain various enzymes. Arginine esterase hydrolase, a thrombin like enzyme, present in viper venom can affect fibrinogen that can form unstable clots that are not affected by factor XIII. Either such clots or disseminated intra-vascular coagulopathy (DIC) could cause arterial thrombotic occlusion.9 Viper venom also contains a complement-dependent vascular damaging factor hemorrhagin. Hemorrhagin can act on microvessels and cause severe vasoconstriction and toxic vasculitis.8 Another mechanism postulated is that of hypotension-induced haemodynamic changes.9 Russell’s viper is responsible for very uncommon problems: pituitary haemorrhages, acute adrenal/ pituitary dysfunction and panhypopituitarism. Little is known of the mechanisms giving rise to these problems.10

Treatment consists of administration of an appropriate antiserum, which not only inactivates unbound toxin but possibly aids in the dissociation of toxin-receptor complex,1 treatment of complications and supportive care. The neurological manifestations of snakebite poisoning depend on the effects of the toxins and enzymes. To effectively manage snakebite poisoning, systematic analysis of possible pathophysiological basis of various clinical manifestations in the given patient is essential.

JMK Murthy

References