Myasthenic syndrome of snake envenomation: a clinical and neurophysiological study

P S Sanmuganathan

Summary
In this prospective study, 65 consecutive patients with neurological manifestations after snake envenomation, were examined in order to describe the natural history of the reversible nature of muscle weakness. Snake envenoming led to a completely reversible muscle paralysis involving the external ocular muscles with sparing of the pupils, muscles of mastication, facial muscles, palatal muscles, neck and proximal limb muscles. The deep tendon reflexes were preserved with no sensory abnormalities. The muscular weakness usually set in within an hour of envenomation and lasted up to 10 days, with fatigability lasting for 12 days. Respiratory muscle paralysis led to ventilatory failure needing ventilation in severely envenomed patients. Motor and sensory nerve conduction were normal with normal resting compound motor action potentials on electromyography. Repetitive nerve stimulation gave rise to a decremental response during high frequency stimulation. The edrophonium test gave negative results. These manifestations are due to abnormalities of neuromuscular transmission and are not typical of myasthenia gravis. As the exact pathophysiology of venom-related neurototoxicity is not known, it is suggested that the neurological manifestations of snake envenoming be designated a myasthenic syndrome. Further studies to isolate the neurotoxin and its mechanism and exact site of blocking at the neuromuscular junction would pave the way for the development of a novel long-acting neuromuscular blocking agent.

Keywords: snake bites; neurotoxicity

Neurotoxic envenoming following snake bite gives rise to a spectrum of clinical manifestations ranging from respiratory failure needing assisted ventilation to mild ptosis with fatigability. Neurological manifestations following snake envenomation have been described in several case histories, each involving motor weakness of varying severity.\(^1\)\(^2\) This study describes, for the first time, results of a prospective study of 65 patients admitted to hospital with systemic envenomation in whom serial neurological examinations were carried out. The objective was to describe the natural history of this reversible muscle weakness.

Patients and methods

PATIENTS
Sixty-five patients with snake envenomation were studied at the Teaching Hospital, Peradeniya, in central Sri Lanka, where many snake-bite victims from the main farming provinces are admitted. Over half (36) the patients identified the snake when they were bitten and another 19 patients had killed the offending snake which was available for identification. Moreover, patients and relatives were shown photographs of venomous and non-venomous Sri Lankan snakes and were carefully questioned about the identity of the snake that had bitten the patient. All patients had local and systemic signs of envenomation.

METHODS
All patients were seen within an hour of admission to hospital. Complete neurological assessment was done on admission and thereafter 12 hourly in patients who came into hospital within 24 hours of the bite, followed by daily assessment until all features had resolved. These neurological assessments were independently done on each occasion, without the bias of knowing the previous examination findings. Nerve conduction study and repetitive nerve stimulation (RNS) was carried out in 18 (28\%) patients. Edrophonium 10 mg was given intravenously to all patients. Haematological and biochemical measurements were made to monitor for coagulation and renal disturbances.

Figure 1  Viper (Viper russelli)
TREATMENT
All patients were treated with a single dose of 10 ampoule Haffkeine Institute polyspecific (Vipera russelli, Naja naja, Echis carinatus, Bungarus caeruleus) antivenom, reconstituted with 100 ml of diluent and further diluted in 500 ml of normal saline, infused intravenously over 30 minutes. Patients who passed less than 400 ml of urine over 24 hours despite rehydration, and where blood urea was rising were managed with fluid restriction, and a salt-free low-protein diet. Peritoneal dialysis was instituted when conservative measures were inadequate. Patients with ventilatory failure due to respiratory muscle weakness had intermittent positive pressure ventilation.

Results
Among the 65 patients with neurotoxic envenoming, 49 (75%) were male. The mean age was 31.5 ± 14.3 years (range 14–66). Most (78%) patients were bitten on the feet with another 18% being bitten on the lower leg. The interval between bite and admission ranged from 25 min to 92 h (median 18 h 35 min). The viper (figure 1) was the offending snake in 36 (55%) patients, cobra (figure 2) in 14 (22%), and krait (figure 3) in five (8%); 10 patients were unable to definitely identify the offending snake.

Symptoms
All patients had fang marks at the site of the bite. Local pain, the commonest symptom, usually started within minutes of the bite. During the next few hours the pain spread upwards to involve the whole limb. Thereafter, 62 patients were nauseated with giddiness and 46 had headache lasting for less than 12 hours; 52 patients complained of diplopia, 22 of whom had difficulty in swallowing; 54 patients vomited. Abdominal pain was noted by 46 patients. No patient lost consciousness.

Signs
Local swelling was observed in 58 (89%) patients, eight of whom (12%) had necrotic wounds at the bite site. Systemic manifestations were present in all 65 patients. Haemostatic failure, as evidenced by spontaneous systemic bleeding, occurred in 14 (22%) patients (bleeding gums in 10 patients and bleeding into the gastrointestinal tract in the other four). Incoagulable blood was the only clinical sign of coagulopathy in 32 (49%) patients. Oliguria with persistent elevation of blood urea developed in 24 (37%) patients, eight of whom needed peritoneal dialysis.

Neurological Manifestations
The neurological manifestations of snake envenoming are shown in table 1. Deep reflexes were preserved with no sensory disturbances. Motor and sensory nerve conduction studies were normal with no specific abnormality in electromyography. Low-frequency RNS (20 Hz) gave variable muscle action potentials with a decremental response in two of the more severely envenomed patients. Higher frequency RNS (50 Hz) produced a decremental response, most marked around 6 days after the bite, which normalised in 10 days. The edrophonium test did not give rise to any convincing improvement in weakness.

Discussion
The snake's venom is stored in glands and injected to kill its natural prey. Snake venom is not a single toxin but a complex mixture of several components, including enzymes, polypeptide toxins, non-toxic proteins, carbohydrates, metals, lipids, free amino acids, nucleotides and bionic amines. Injection of these components with their various actions leads to the immediate death of small animals. However, when a snake bites a human, the dose of venom in relation to body size is too small to produce this dramatic effect. Snake envenoming of humans gives rise to an assortment of clinical manifestations which occur insidiously.

Although the procoagulants which activate the clotting cascade do not cause massive fatal intravascular coagulation in human victims,
they do cause the deposition of microthrombi and activation of the fibrinolytic system. The clinical result of procoagulant activity is a consumption coagulopathy, resulting in incoagulable blood in 49% of patients. Once the patient's blood is defibrinated, the further action of haemorrhagins, which damage vascular endothelium and cause platelet abnormalities,

leads to spontaneous systemic haemorrhage in 22% of patients. Microthrombi deposition and vasoconstriction of renal vessels with hypotension contribute to acute tubular necrosis. Activation of the fibrinolytic system which gives rise to intravascular haemolysis, and disseminated intravascular coagulation, together with the direct nephrotoxic action of venom, lead to acute renal failure in 37% of patients. Proteolytic enzymes present in snake venom are responsible for the local necrosis which occurs in 12% of patients, while increased vascular permeability causes immediate local swelling and pain, observed in 89% of patients in our series.

This study shows the diversity of clinical manifestations after snake envenomation, with special emphasis on neurotoxic manifestations. Identification of the snakes in this study was done using photographs and verbal descriptions and we do not therefore intend to correlate any clinical findings with the snake species. This study describes the waning nature of the muscle weakness which suggests the reversible action of snake neurotoxin. However, the onset of weakness was not observed in this study, as many patients came to hospital while they were developing the paralysis. All 63 patients had ptosis with fatigability and weakness of neck flexion, starting with ocular and oropharyngeal weakness that progressed to involve proximal limb muscles in 58% of patients. This syndrome of spared pupillary response, no sensory or cerebral abnormalities and preserved deep reflexes, is probably due to abnormal neuromuscular transmission. The motor weakness was completely reversible and lasted for a mean period of 5 days. Two patients envenomed by the common krait (Bungarus caeruleus) had reversible respiratory muscle paralysis needing assisted ventilation for 18 and 48 hours, respectively. We have previously described the need for ventilation in a patient envenomed by the Ceylon krait (Bungarus ceylonicus). Snake venom neurotoxin causing muscle weakness due to rhabdomyolysis has been described. Rhabdomyolysis was excluded by the absence of generalised muscle pain, myoglobinuria and normal serum creatinine phosphokinase and aspartate transaminase activity.

<table>
<thead>
<tr>
<th>Proximality</th>
<th>External ophthalmoplegia</th>
<th>External ophthalmoplegia</th>
<th>External ophthalmoplegia</th>
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</thead>
<tbody>
<tr>
<td>Weakness of neck flexion and proximal limb muscles</td>
<td>common</td>
<td>common</td>
<td>uncommon</td>
</tr>
<tr>
<td>Reflexes</td>
<td>preserved</td>
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<td>negative</td>
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<tr>
<td>Edrophonium test</td>
<td>positive</td>
<td>negative</td>
<td>decrement at low frequency</td>
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<td>RNS</td>
<td>decrement at low frequency</td>
<td>decrement at high frequency</td>
<td>decrement at low, facilitation at high frequency</td>
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Myasthenia gravis, Lambert-Eaton myasthenic syndrome, and snake envenomation share similar features, such as ptosis with fatigability, external ophthalmoplegia, and weakness of masticatory, facial and palatal muscles, but there are also some interesting differences, shown in table 2.

Snake venom neurotoxins that bind to acetylcholine receptor sites on the motor endplate produce effects similar to those of curare and myasthenia gravis.

Another group of neurotoxins with phospholipase A2 bind presynaptically, thereby depressing transmitter release, and are completely resistant to anticholinesterases.

In our patients, high frequency RNS gave rise to a decremental response which was not apparent with low frequency RNS. Clinical trials testing anticholinesterase drugs have demonstrated both favourable and unfavourable results. Venom components are species-specific and therefore, there is a variance in the response to anticholinesterase drugs. Patients in our series are postulated to have had predominantly presynaptic blocking venom components, as they showed no improvement with edrophonium. However, the decremental response on high frequency RNS needs further explanation.

Conclusions

Clinical observations on these patients point to a characteristic myasthenic distribution of muscle weakness involving external ocular, masticatory, facial, palatal, neck flexor and proximal limb muscles. As RNS at high frequency led to a decremental response and the outcome of edrophonium testing was negative, the features can best be described as a myasthenic syndrome, at least until the pathophysiological mechanisms of the neurological manifestations are worked out.

Further laboratory studies are necessary to isolate and characterise the neurotoxic components of snake venom, which will allow us to elucidate the molecular basis of the reversible proximal muscle weakness. This will pave the way for the development of a novel long-acting neuromuscular blocking drug. In this context it is worth noting that the five patients envenomed by B caeruleus, two of whom needed assisted ventilation, had only neurotoxic features. Therefore, it would be prudent to isolate the neurotoxic components from krait venom first, as this seems to lack the components of other snake venoms which cause haemostatic, renal and vasoactive dysfunction.
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