Two Cases of Early Morning Neuroparalytic Syndrome (EMNS) in the Tropics - Masquerading as Brain Death

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Introduction

Snake bite is a common problem seen in India especially in rural parts, and is associated with a high rate of mortality if not diagnosed and treated in time. Neurotoxicity from elapid bite may masquerade as early morning neuroparalytic syndrome (EMNS) and diagnosis at the initial stage is challenging as these patients seldom have bite marks or history of being bitten. We are reporting a series of two cases who presented as EMNS with absent brain stem reflexes, mimicking brain death. After ruling out other causes of similar clinical presentations and based on a positive Neostigmine challenge test, both patients were empirically treated with a standard regimen of anti-snake venom (ASV), along with broad spectrum antibiotics, anti-infective therapy. These cases highlight the need to watch out for Elapid bites (especially Krait), in a tropical country like ours. These cases who presented as EMNS with absent brain stem reflexes, mimicking brain death. The first case was noted to have neck muscle weakness and respiratory distress and was referred to nearby Medical college in Aligarh. He became stuporous during the road journey and was intubated on arrival at the Medical college as he was found drowsy with a low GCS of 8/15 along with pupillary abnormalities and was desaturating despite oxygen therapy. His initial hematological and biochemical parameters were normal and a CT head did not reveal any abnormality. He was managed with broad spectrum antibiotics, anti-infective therapy and ventilatory support. However over the next two days he became deeply comatose with a GCS of 3/15, dilated fixed pupils and absent respiratory efforts.

Abstract

Neurotoxicity from elapid bite may masquerade as early morning neuroparalytic syndrome (EMNS). We are reporting a series of two cases who presented as EMNS with absent brain stem reflexes, mimicking brain death. The first case was being considered for potential organ retrieval when the diagnosis was revised, and he recovered completely with Anti-snake venom (ASV). The second patient developed severe anaphylaxis to ASV, which made continuation of the empirical therapy in a comatose patient very tricky. She gradually tolerated a low dose ASV infusion under steroid and adrenaline cover, with reversal of paralysis and coma. Both the patients showed excellent recovery post ASV treatment. A simple bedside Neostigmine challenge test and timely ASV therapy can save many helpless patients of EMNS from certain death.

Case - 1

A 38 year old driver, with no previous co-morbidities, was on leave at his hometown Aligarh. He had an alcohol binge with his friends in the evening and fell asleep in the courtyard at home around 11 pm. He woke up at morning 3 am complaining of abdominal pain and vomiting which was attributed to alcohol by his wife and managed with lemon juice and antacids at home. However, he could not go back to sleep and remained restless throughout the night. By 6 am he complained of difficulty in swallowing and double vision and was taken to a local doctor. There he was noted to have neck muscle weakness and respiratory distress and was referred to nearby Medical college in Aligarh. He became stuporous during the road journey and was intubated on arrival at the Medical college as he was found drowsy with a low GCS of 8/15 along with pupillary abnormalities and was desaturating despite oxygen therapy. His initial hematological and biochemical parameters were normal and a CT head did not reveal any abnormality. He was managed with broad spectrum antibiotics, anti-infective therapy and ventilatory support. However over the next two days he became deeply comatose with a GCS of 3/15, dilated fixed pupils and absent respiratory efforts.

He was transferred to a tertiary care hospital in Delhi Cantt on day three, on a portable ventilator with a diagnosis of Brain Death (cause unknown). At presentation, the patient was comatose with GCS of 3/15 on CMV mode ventilation. He had pyrexia of 100°F, pulse of 120/min regular and blood pressure of 140/78 mm of Hg. There was no skin rash or bite marks noted. Neurologic examination revealed normal ocular fundi with a soft neck but absent superficial and deep tendon reflexes and mute plantar response. All brain stem reflexes were absent (both pupil 8mm dilated and non reactive, no reflex ocular movements, and absent corneal/ pharyngeal reflex). Chest examination revealed good air entry bilaterally (on Ventilator) with vesicular breath sounds and scattered coarse crackles in right infrascapular and axillary region. Cardiovascular and abdominal examination were not contributory. Urgent capillary glucose by glucometer was 151 mg% and ECG was normal. Arterial blood gas showed pH of 7.36, pO2: 163mmHg, pCO2: 55.3 mmHg, HCO3-: 30.7 mEq/L, Na+: 142 mEq/L, K+: 3.9 mEq/L. An urgent CECT head was normal and he was admitted to ICU on ventilator for further evaluation of the cause for acute encephalopathy. He remained in the same neurologic state for next 24 hrs and only positive investigation being, elevated TLC of 16,700/cu mm with 90% polymorphs and chest X ray showing non homogenous soft alveolar opacities in right lower zone, suggesting a probable health care associated pneumonia. His CSF study showed proteins of 20 mg% and no cells. CSF...
India ink stain and latex agglutination for cryptococcal antigen were negative. CSF HSV PCR was also negative. CSF ADA levels were normal. Serologic studies for HIV, HBsAg and HCV were negative. A broad differential diagnosis was considered at this stage including AIDP/Myasthenic crisis with hypoxic encephalopathy, paralytic forms of rabies, poisoning with psychotropic agents and neuroparalytic snake bite. In the mean while an overseas transplant team member initiated dialogue for further brain death testing and organ donation considering a young healthy patient with clinical diagnosis of Brain death. However this error was quickly corrected. Since the patient did not have a clear cause of brain stem dysfunction and had normal neuroimaging, he did not meet the first basic criteria for potential brain death testing. Since the first two diagnoses of HIE carried a poor prognosis and a toxicology screen would take time to obtain, it was decided to give a simple bedside neostigmine challenge to look for reversible neuromuscular blockade. Immediately after 1.5 mg IV neostigmine, the patient for the first time showed eyelid movements along with few weak inspiratory efforts on the ventilator tracing. This raised the suspicion of a possible elapid bite with severe neuroparalysis. Although the complete absence of brain stem reflexes was very odd. However a quick literature search and review confirmed similar case reports of unexplained neuroparalysis and severe brain stem depression in elapid bites from India and Sri Lanka. It was thus decided to give him polyvalent anti-snake venom (ASV). He was given 100 ml of reconstituted ASV every 8th hourly for next 72 hrs along with Inj Neostigmine 1.5 mg IM 6th hourly. He showed progressive improvement in muscle power with return of spontaneous limb and respiratory movements over next 3 days. He was weaned off ventilator five days after starting ASV and regained full consciousness, when he was shifted to medical ward. He confirmed the high incidence of elapid snakes in his area and also having slept outdoor on the floor after alcohol binge, increasing many fold the risk of snake bite. While he gradually regained grade 4/5 muscle power over the next four weeks and started walking without support, his pupils remained dilated and fixed at 8 mm. He was sent on leave for six weeks which was uneventful and he regained grade 5/5 power with return of pupillary reflexes when examined after sick leave. He went back to full duties within 3 months of being declared brain dead and being on the list of transplant team for organ donation!

**Case - 2**

A 27 year old mother, nursing 6 month old twin babies, was rushed to emergency room in a comatose state at 0730 h in the morning. She had slept normally the previous day at 2330 h and did not get up at night to feed her babies. She continued to sleep beyond 6 am which was her usual time of awakening. At 0700 h, she was noticed by her mother to have heavy breathing and in an unresponsive state. She was immediately brought to emergency department of our hospital. On arrival at emergency room, her GCS was 6/15 (E1V2M2) with blood pressure 130/80 mm Hg, heart rate 102/min, respiratory rate 28/min and random capillary glucose level was 112 mg/dL. She was immediately shifted to ICU. She had optimal oxygen saturation despite tachypnea, but her GCS deteriorated to 5/15 (E1V2M2) over the next hour in ICU. There was no skin rash or injury marks or any signs of meningeval irritation. Her ECG was normal and arterial blood gas showed normal parameters. Her Ryles tube (RT) aspirate was clear and there was no smell of OP compounds or alcohol. She was kept on continuous RT aspiration to keep stomach empty. Her urine examination for beta HCG and toxicology screening were negative.

On detailed CNS evaluation she had depressed brain stem reflexes, pupils were 8 mm and only sluggishly reacting to light, corneal reflex and doll’s eye were absent and pharyngeal gag reflex was absent. She had generalized hypotonia with depressed deep tendon reflexes and bilateral plantar showing extensor response. She had normal vesicual breathing in all chest areas. Cardiovascular and abdominal examination were normal. Her baseline investigations showed normal hemogram and biochemical parameters. An urgent NCCT head was also normal. She was managed with anti-epileptics, antivirals (Acyclovir), considering seizures with post ictal state or viral encephalitis as possibilities. She underwent MRI and MRA brain to look for any signs of encephalitis or posterior circulation stroke/CVT, but no abnormality was found. Her urgent EEG showed diffuse background slowing, but no epileptiform discharges.

Every investigation only added to the mystery of her encephalopathy. A lumbar puncture and CSF examination was also normal. Meanwhile, her GCS dropped further to 4/15 with laboured breathing and pupils became non reactive to light. She was intubated and put on SIMV mode of ventilation, about six hours after coming to hospital with no diagnosis. Considering the authors previous experience with a similar case, Elapid bite was strongly considered at this stage as a cause of rapidly evolving EMNS and absent brain stem reflexes mimicking brain death.

She was subjected to a neostigmine challenge test and for the first time since admission, she showed eyelid movements along with lifting of eyebrows. This indicated the strong possibility of neuro-paralytic snake bite (Elapids). A literature review confirmed case reports of krait bite (Elapids) from South Mumbai, where she was staying, although viper bites were by and far more common. In view of absence of an alternate explanation and strong clinical suspicion, it was decided to offer her empirical polyvalent anti-snake venom (ASV).

A standard test dose of 01 ml of diluted ASV was given IV, however it triggered sudden tachycardia (130-140 beats/min) and fall in blood pressure (80/60 mm Hg systolic) along with a diffuse erythematous skin rash. She responded to IV hydrocortisone and pheniramine. Clearly she was reacting to the ASV, and we had to decide on continuing an empirical therapy which was triggering hemodynamic instability and anaphylaxis. However considering the lack of other therapeutic options and our strong clinical suspicion we took the NOK into confidence and started a very low dose ASV infusion at the rate of on 0.5 ml/h (reconstituted ASV) under steroid and anti-histamine cover with adrenalin as stand by. ASV infusion had to be stopped thrice in the first four hours due to hemodynamic instability and adrenaline was used once due to sudden fall in BP. But she started tolerating the very low dose infusion after 06 hours. Infusion rate was gradually doubled every hour thereafter to a maximum of 10 ml/h.
She opened eyes about 20 hours after starting ASV. She showed steady motor recovery in the form of spontaneous limb movements by 24 hours when ASV was stopped (Total about 250 ml). She regained her sensorium and was extubated 36 hours after ASV. She started walking with support after 72 hours and thereafter showed steady improvement in clinical status. On further enquiring, she gave history of visit to the society park and a long walk in grass without footwear, the evening prior to her hospitalization. She was not sure about any bite. She was discharged home with twins in her arms, 6 days after being clinically brain dead, and responding to ASV therapy, which almost killed her due to anaphylaxis!!

**Discussion**

Snake-bites are well-known medical emergencies in many parts of the world, especially in rural areas. India is estimated to have the highest snake bite mortality in the world. Agricultural workers and children are the most affected. World Health Organisation (WHO) estimates place the number of bites to be 83,000 per annum with 11,000 deaths. In India, the common species of snakes seen are the Elapidae which includes common cobra, king cobra and krait, Viperidae which includes Russell’s viper, pit viper and saw-scaled viper and Hydrophidae (the sea snakes).


Neuroparalysis in a snake bite occurs as a result of blockade of neuromuscular transmission. Toxins from cobra venom act mainly postsynaptically whereas those of krait venom act mainly presynaptically. Neurotoxicity following krait bite is common, manifesting frequently as respiratory muscle paralysis. The krait venom competes with acetylcholine at the neuromuscular junction post-synaptic receptors leading to neuromuscular paralysis (Figure 1). The venom by its direct neurotoxic effect on the brain could produce alteration of level of consciousness ranging from drowsiness to deep coma. Neurotoxicity from the elapid bite may manifest as early morning neuroparalytic syndrome (EMNS) or even as locked-in syndrome. Patients presenting as EMNS do not have bite marks on their body and hence the diagnosis may be complicated. The time lag between the bite and onset of paralysis is usually 4–12 hours. The earliest manifestation is ptosis followed by external ophthalmoplegia. Paralysis then progresses to involve muscles of palate, jaw, tongue, larynx, neck, and muscles of deglutition - usually but not strictly in that order. The proximal muscles of the limbs are involved earlier than distal, and there can be complete quadriplegia and ‘locked-in’ state. Patients with acute respiratory failure are categorised as severe envenomation. Recovery starts in the reverse order and the median time of onset for recovery of respiratory failure is 2 days.

Patients, like the first case we have presented, with ‘locked-in’ state and absent pupillary reflexes are uncommon. Internal ophthalmoplegia seen in these patients can plausibly be attributed to the autonomic dysfunction. It is important that emergency physicians recognise the ‘locked-in’ syndrome, so as to prevent the dangerous error of diagnosing brain-death. The diagnosis of brain-death requires a clear and evident cause of CNS insult/ disease, along with documentation of coma, absence of brain-stem reflexes, and unresponsive apnea, in the absence of conditions that mimic brain death like severe electrolyte and acid-base disturbances, drug intoxication, neuromuscular blocking agents, etc. In fact, confirmatory tests like cerebral angiography, electroencephalography, etc, are recommended in situations like ‘locked-in’ syndrome, where a diagnosis of brain death is difficult to establish.

Anti-snake venom (ASV) is a specific antidote to snake venom actions, however, there are no clear guidelines on the optimal dose in management of patients with severe envenomation and doses as high as 1400 mL have been used empirically in the hope of early recovery. Some studies have addressed the issue of ASV dosage, but not specifically in patients with severe neuroparalytic envenomation. The use of ASV is generally safe and only rarely have fatalities been reported. The incidence of reactions to ASV has varied from 4–8%. The reactions can range from pyrogenic reactions (mild) to anaphylactic shock (severe) and can be prevented by premedication with subcutaneous adrenaline, intravenous hydrocortisone, and anti-histamines. It is important to remember that anaphylaxis does not mean stopping ASV, but giving it slowly and carefully to anaphylactic shock (severe) and can be prevented by premedication with subcutaneous adrenaline, intravenous hydrocortisone, and anti-histamines. It is important to remember that anaphylaxis does not mean stopping ASV, but giving it slowly and carefully with monitoring under steroid and adrenaline cover. We used a similar low dose empirical regimen in our second case, which she tolerated and then responded very well despite initial severe anaphylaxis.

In our two cases, initially the possibility of brain death secondary to prolonged hypoxia prior to
hospitalisation was considered, as patient had rapidly evolving neuroparalysis followed by coma, absence of brainstem reflexes and apnea. However a high index of suspicion, with a positive neostigmine challenge and residence in a snake infested region, helped make the diagnosis of snake bite.

Case 1 is the first case report where the patient was diagnosed as brain dead and almost went under the transplant surgeon’s knife before timely diagnosis and recovered steadily after starting ASV with complete reversal of neuroparalysis in six weeks. Case 2 highlights the need to continue empirical ASV therapy, even in the setting of severe anaphylaxis, with adequate steroid and adrenaline cover.

Conclusion

In conclusion, patients with unexplained neuroparalytic syndrome or EMNS and depressed brain stem reflexes, in tropical areas where snake bites are endemic, should attract the attention of emergency room physicians to the possibility of elapid snake bite (especially Krait since its bite marks are not visible). After carefully ruling out other common causes of acute encephalopathies, one should consider empirical ASV therapy even when no history of snake bite is available. Early and energetic ASV therapy even in patients with anaphylaxis to ASV, is associated with excellent outcomes.

References