CASE REPORT

Hypertensive encephalopathy with locked-in syndrome mimicking brain death: An unusual case of Krait envenomation with literature review.

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Abstract

Introduction: Neuroparalytic snake bite is a serious life-threatening hazard all over the world, especially in tropical countries of South-East Asia. But it is one of the most neglected tropical diseases. Patients can present with envenomation signs without a history of snakebite or an identifiable bite mark. Apart from neuroparalysis**,** symptoms of autonomic dysfunction can also be seen with krait envenomation.
Case Report: 11-year-old girl presented with early morning sudden onset altered sensorium. On examination found to have absent spontaneous respirations, severe hypertension, dilated pupils, and absent brainstem reflexes, so labeled as probable brain death. Later with control of hypertension, she was able to respond by blinking but had severe neuroparalysis. There was no evidence of snakebite but with a strong suspicion of krait envenomation, anti-snake venom was given empirically and continued ventilatory support, following which child had a complete recovery.
Discussion: As the majority of krait bites occur during sleep and due to its painless nature, they often go unnoticed. Also, krait bite leaves very fine puncture marks and the local reaction is markedly absent, so fang marks couldn't be easily identified. Autonomic dysfunction following krait envenomation can present as abdominal pain, vomiting, sweating, mydriasis, fluctuation of heart rate and blood pressure, and paralytic ileus. In severe krait envenomation, complete paralysis of all voluntary muscles leads to quadriplegia and anathria which resembles locked-in syndrome. Locked-in syndrome when associated with internal ophthalmoplegia can mimic brain death.
Conclusion: Snakebite should be considered in the differential diagnosis of unexplained neuroparalysis and hypertension. Envenomation should not be excluded by the absence of a history of snakebite or identifiable bite mark.

Keywords: Snakebite, Hypertension, Coma.

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INTRODUCTION

Neuroparalytic snake bite is a serious life-threatening hazard all over the world, and especially in tropical countries of South-East Asia. Patients can present with envenomation signs, without a history of snakebite or an identifiable bite mark.(1) Apart from neuroparalysis**,** symptoms of autonomic dysfunction can also be seen with krait envenomation. A strong clinical suspicion should be there otherwise these atypical presentations could be misdiagnosed, leading to delay in the appropriate treatment. Autonomic dysfunction and locked-in syndrome can be seen rarely with neurotoxic snakebite mimicking brain death, leading to withdrawing of support which could be fatal. In this case report we describe a child, who presented with hypertension, neuroparalysis, and absent reflexes mimicking brain death, without a history of snakebite and got better with anti-snake venom (ASV) administration and supportive care. We also review the varied and unusual presentations of krait envenomation described in the literature.

CASE REPORT

An 11-year-old girl, apparently normal previously, was sleeping on the floor and woken up at 5 AM with the complaint of non-colicky abdominal pain and was followed by non-bilious non-projectile vomiting. Later she had breathing difficulty. Parents noticed that she was gradually becoming drowsy and not able to speak or move limbs. She was initially responded to the commands by the partial opening of the eyes. Later she became completely unresponsive with shallow breathing efforts. She reached the nearby hospital at around 10 AM. She was found to be unconscious, gasping, and hypoxic, so she was intubated there. After stabilization of vitals, she was transported to our

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unit with bag and tube ventilation. She reached our unit at 2 PM and the transport was uneventful. On examination found to have tachycardia (140/min), hypertension (180/120 mm Hg), no spontaneous respirations, copious ET and oral secretions, bilateral crackles, and hepatomegaly (liver span - 14cm). Central nervous system (CNS) examination revealed Glasgow coma scale (GCS) E1VTM1, bilateral dilated (7mm) nonreactive pupils, generalized hypotonia, areflexia including absent dolls eye reflex, and cough reflex, and mute plantars. No history of fever/ seizures/ headache/ blurring of vision/ trauma/ bleeding manifestations/ drug intake/ dog bite/ ingestion of poisonous substances/ envenomation.

Initial differential diagnoses thought were CNS pathology (encephalitis/ stroke/ bleed) with raised intracranial pressure leading to hypertension or hypertensive encephalopathy (secondary to renal/ drugs/ intoxications) with additional hypoxic encephalopathy, and with probable brain death. As the history is acute and there is no history of significant hypoxia to explain this sudden brain death, we decided to treat the child. After adequately sedating her with midazolam and fentanyl, transient hyperventilation was done along with a bolus dose of 3% normal saline, there is no reduction in blood pressure. In computed tomography of brain there was no evidence of cerebral edema/ bleed/ infarct. So we thought that primary CNS pathology could be unlikely. So she was managed as hypertensive encephalopathy, started on sodium nitroprusside (SNP) infusion, and attained gradual reduction of blood pressure. Blood sugar, renal/ liver function tests, and serum electrolytes were normal. Ultrasonic imaging of kidneys and renal vessels was normal, urine examination revealed no proteinuria/ hematuria. Echocardiography revealed severe left ventricular (LV) dysfunction (Ejection fraction 25%). With hypertension, LV dysfunction, and increased secretions, scorpion bite envenomation was also thought of as a possibility, but there is no history of bite or local swelling suggestive of scorpion bite.

After 12 hours of admission, blood pressure was 150/100 mmHg and the child started opening eyes, but had ptosis. In the next few hours, she responded to commands by blinking, but there were no limb movements. Detailed CNS examination at this time revealed GCS- E4VTM1, ptosis, dilated (6mm) and nonreactive pupils, external ophthalmoplegia, absent dolls eye reflex, quadriplegia (muscle power 0/5 in all limbs) with hypotonia and areflexia. So she was diagnosed to have the classical locked-in syndrome of peripheral etiology. Differentials kept were neurotoxic snakebite, Guillain-barre syndrome (GBS), myasthenic crisis, and botulism. There is no history of snakebite as well as no identifiable fang marks on the body. Nerve conduction study was done which was normal ruling out GBS. There was no significant history suggestive of myasthenia or botulism. A literature review was done and found cases reported with a similar presentation due to krait envenomation. So after reasonably ruling out other differentials and with a strong suspicion of krait envenomation 10 vials of ASV were given empirically. After 1 hour another 10 vials of ASV were given as there is no response according to Indian snakebite protocol. After 24 hours of ASV administration power gradually improved to 3/5, ptosis improved, pupils were 4mm with sluggish reaction, blood pressure normalized so SNP was weaned and stopped. After the next 48hours, power was 4/5, no ptosis, pupils were bilateral 3mm with normal reaction to light, LV function improved. Extubated on day 4 and was discharged on day 6 with normal sensorium, almost normal power, and normal LV function.

DISCUSSION

Even though snakebite is a common medical emergency worldwide, it is one of the most neglected diseases. It remains an underestimated cause of occupational or accidental death in the modern world. The total number of snakebites exceeds 5 million/ year with a mortality of 1.25 million each year across the globe (1). The three important families of venomous snakes in South East Asia are Viperidae, Elapidae, and Colubridae. Elapidae includes cobras, kraits, death adders, brown, and black snakes and sea snakes which are neurotoxic. Composition and antigenicity of the snake venom vary widely between and within species, between sexes, with age, with the season, and throughout the geographical range leading to varied symptomatology and severity (1).

Neurotoxicity of krait envenomation mainly present as neuromuscular paralysis which is classically a descending paralysis starting with ptosis and external ophthalmoplegia and then facial and bulbar muscle weakness and finally involving respiratory and limb muscles. Autonomic dysfunction is less common and can present as abdominal pain, vomiting, sweating, mydriasis, fluctuation of heart rate and blood pressure, and paralytic ileus (1). Alpha and beta bungarotoxins are the clinically important constituents of krait venom. Alpha-bungarotoxin binds to post-synaptic muscle acetylcholine receptors and produces an irreversible, non-depolarizing block. Beta bungarotoxin binds to the presynaptic motor nerve terminals irreversibly, leading to depletion of synaptic acetylcholine vesicles, the impaired release of acetylcholine, and later, degeneration of the motor nerve terminal (2). Clinical recovery is slow even after ASV administration, as it is dependent on regeneration of the nerve terminal and formation of a new neuromuscular junction (2). The mechanism for autonomic dysfunction seen in krait envenomation was unclear, the possible explanations were blockade of neuronal acetylcholine receptors at the postsynaptic level in autonomic ganglia, thus reducing the parasympathetic activity and also blockade of presynaptic alpha 2 adrenoreceptors, releases the inhibition on the neurally mediated release of norepinephrine thus causing sympathetic activation (2).

The common krait (Bungarus caeruleus) is nonaggressive, nocturnally active and enter houses in search of its prey such as rats. Bites occur when they are disturbed by the sleeping person accidentally. Usually krait bite is painless with very fine puncture marks and without local tissue reaction, so fang marks couldn't be easily identified (1). As the majority of bites occur during sleep and due to its painless nature, Krait bite often goes unnoticed. Slowly the venom will take its effect and patients experience symptoms early in the morning when they wake up. This explains the absence of evidence for snakebite in our child. If clinicians are not aware of these,

patients presenting with symptoms of envenomation but with no history of snakebite and absent fang marks will be misdiagnosed to some other condition eventually delaying the appropriate treatment.

Various case reports and studies have been published over the years enlightening the varied and unusual presentations of krait envenomation. Saini et al. first described early morning neuroparalytic syndrome (EMNS) which is a rare presentation of krait envenomation seen in slum dwellers, who sleep in the open environment outside the houses (3). These patients present to the hospital with early morning onset ptosis and neuroparalysis without a history of snakebite and unidentifiable bite marks. After this so many authors have described EMNS in their case reports and all reported good outcomes with ASV and supportive care (4,5). In a prospective interventional study conducted by Kshirsagar et al., 41 children presenting with acute onset early morning neuroparalysis but without a history of snakebite and identifiable fang mark, fitting to EMNS, has been treated with empirical ASV after ruling out other medical conditions and all are responded well suggesting possible krait envenomation (6). In a recent retrospective study done by Samprathi et al. described 51 cases of EMNS in children (7). In a prospective study done by Kularatne on krait bite in Srilanka, ptosis (70%) was the commonest symptom identified followed by dyspnea/ abdominal pain (68%) and then limb weakness/ decreased consciousness (64%). Abdominal pain was the initial presenting symptom. Autonomic dysfunction was seen in 60%. Myalgia and paresthesia occurred less commonly. 31% were unaware of the bite and in 17% there is no visible fang mark (8).

Locked-in syndrome (LIS) is a rare neurological disorder where the patient is wakeful and aware, with intact cognitive function but unable to communicate. It is due to complete paralysis of voluntary muscles resulting in quadriplegia and anarthria. It is of three types, 1) classic LIS, where vertical eye movements or blinking is preserved, 2) incomplete LIS, where remnants of other voluntary movements are there, and 3) total LIS, where there is a complete absence of all movements. LIS is caused by damage to ventral pons, commonly by ischemia, demyelination, hemorrhage, or encephalitis. It can also be caused by peripheral causes such as severe GBS and neuromuscular junction blockade secondary to myasthenia crisis, toxins, and snakebite (9). There are many case reports reporting krait envenomation presenting as LIS (10–13).Total LIS presenting with mydriasis and loss of brain stem reflexes mimics brain death which can be rarely seen in elapid snake bite. Routine brain death criteria will be easily met in these cases. This causes a dilemma for caregivers to withdraw the ongoing support. In such cases, ancillary testing methods like electroencephalography, transcranial doppler ultrasonography, cerebral angiography, positron emission tomography, and radionucleotide imaging will be helpful to confirm or refute the diagnosis of brain death (14). Shukla et al. reported total LIS with mydriasis mimicking brain death in an 11year old boy following a documented krait bite and subsequently with ASV and supportive measures child recovered after 86 hours (15). Dayal et al. also reported a similar presentation in a child (16). Anadure et al. described 2 adult cases of EMNS masquerading as brain death (17). Several authors reported krait envenomation presenting with hypertension and coma (18–22). In our child the combination of hypertensive encephalopathy with LIS was the reason for brain death presentation. This is justified by the fact that the child's sensorium normalized rapidly after hypertension control even before ASV administration. To the best of our knowledge, this was not reported previously in the pediatric population.

Other rare atypical presentations described in the literature following krait envenomation are cerebellar ataxia, encephalopathy, leukoencephalopathy, acute disseminated encephalomyelitis, and GBS (2,23–28). These manifestations are thought to be secondary to immune-mediated damage which was triggered either by the venom or ASV. Cerebrovascular events are also described, mostly with viper bites (23).

ASV and supportive care remain the mainstay of treatment for snakebite. ASV contains venom neutralizing antibodies [usually pepsin-refined F(ab')2 fragment of the whole IgG], which are purified from the plasma of a horse, donkey, or sheep, after hyper-immunizing them with snake venom. In India, polyvalent ASV is manufactured from horses using the venoms of the four most important snakes (Indian cobra, Naja naja; Indian krait, Bungarus caeruleus; Russell's viper, Daboia russelii; saw-scaled viper, Echis carinatus). Even though there are raising concerns regarding efficacy, ASV treatment should be initiated as soon as it is indicated. It has been reported that if systemic envenomation is there, ASV can reverse it even when administered after several days (1). Supportive care in the form of mechanical ventilation is the mainstay in saving the lives of krait envenomation victims. In resource-limited settings, even the manual ventilation is life-saving (29). Recently there was a case report from Vietnam describing the usefulness of alpha chymotrypsin in reversing the neuroparalysis caused by Bungarus multicinctus (30).

CONCLUSION

Hypertensive encephalopathy and locked-in syndrome are rare presentations of krait envenomation which can mimic brain death. Krait envenomation should be kept in the differential diagnosis, even in the absence of history of snakebite or an identifiable bite mark. Timely administration of ASV, and continuing supportive measures till the venom effects wear off will eventually lead to complete recovery.

LIMITATION

Laboratory confirmation by immunoassay of the venom antigen was not done due to the lack of availability of the service. No other possible explanation for the clinical scenario, dramatic improvement with ASV, and evidence from literature strongly supports krait envenomation.

Take home points:

1. Snakebite should be considered in the differential diagnosis of unexplained altered sensorium, neuroparalysis,

hypertension, and abdominal pain in snakebite endemic areas.

2. Envenomation should not be excluded by the absence of fang marks or no history of snakebite.

3. Locked-in syndrome can mimic brain death, so look for all treatable causes in unexplainable brain death and use ancillary testing methods in case of suspicion.

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