

NEUROTOXIC SNAKEBITE CASES WITH ROLE OF IMAGINGUpendranath Upadhyay¹, Udit Upadhyay², Nayan Kishore Mohanty³, Sarat Kumar Behera⁴¹Professor and HOD, Department of Radiology and Imaging, Hi-Tech Medical College and Hospital, Bhubaneswar.²Postgraduate Student, Department of Orthopaedics, Hi-Tech Medical College and Hospital, Bhubaneswar.³Principal and Professor, Department of Forensic Medicine and Toxicology, Hi-Tech Medical College and Hospital, Bhubaneswar.⁴Professor and ICU In-Charge, Department of Pulmonary Medicine, Hi-Tech Medical College and Hospital, Bhubaneswar.**ABSTRACT****BACKGROUND**

Snakebite cases in India is around 6,00,000 to 16,00,000 with deaths around 11,000 to 25,000 (in Odisha around 1000 snakebite deaths per annum). Highest occurrence is seen in monsoon (June to September) probably due to increased exposure to traditional agriculture practice. Imaging plays a limited, but immortal roles in cases with diagnostic dilemma.

MATERIALS AND METHODS

Total snakebite cases admitted to Hi-Tech Medical College from January 2016 to September 2017, and out of these, the number of cases undergone different imaging studies like x-ray, USG, Doppler, CT scan, CT angiography and MRI studies were included under study. The findings were analysed in background of pathophysiology and toxic action of neurotoxic snake venoms.

RESULTS

Out of 52 cases admitted in Hi-Tech Medical College, Bhubaneswar, the total 12 cases (23%) were undergone imaging study. Out of these, 3 cases sent for MRI study to outside diagnostic center due to non-availability of MRI facilities. Other imaging studies are done in our hospital.

CONCLUSION

Imaging in few cases plays important and decisive role in situations with diagnostic dilemma in prolonged neurological symptoms, delayed neurological complications in local complications and secondary systemic complications.

KEYWORDS

Ach-Acetylcholine, nAChRs- Nicotinic-Acetylcholine Receptors, AChEIs- Acetylcholinesterase Inhibitors, SNARE- Soluble N-ethylmaleimide-Sensitive Factor Attachment Receptors, NMJ- Neuromuscular Junction, 3FTxs- Three Finger Toxins, PLA2s- Phospholipase A2 Toxins.

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BACKGROUND

Snakebite is a neglected tropical disease of global importance.¹ It has been estimated that annually at least 1.2 million snakebites with 42,000 envenoming and 20,000 deaths occur worldwide.² Snakebite-related mortality is highest in resource-poor countries and is directly related to socioeconomic indicator of poverty. The highest burden of morbidity and mortality related to snakebite are seen in rural poor communities of tropical countries in South Asia, South East Asia and Sub-Sahara Africa.^{3,4} In India, the total snakebite cases are reported 6,00,000 to 16,00,000 with death figures 11,000 to 25,500.⁵ Coming to statistics in Odisha, the exact figures are not known. It is estimated that

2,500 to 6,000 cases of snakebite occurs in Odisha, and out of them, 400 to 900 cases dies (around 1000 snakebite deaths per annum).⁶ But, the actual figures likely to be much higher. Data from million deaths study in India estimates that snakebite deaths are 30-fold higher than recorded in hospital returns.⁷ The highest snakebite cases are recorded in monsoon (June to September) mostly in nights. This is because of increased exposure to snakes due to traditional agricultural practice. Besides this, lack of good health service, poor access to available services, influence of health seeking behavior on accessing the available healthcare services and lack of effective antivenom and it's under supply and blind beliefs and cultural practices by local traditional healer contribute more for increased number of snakebite death cases.⁸ In the above scenario, the state has a challenging role to reduce the figures of the morbidity and mortality in snakebite cases.

MATERIALS AND METHODS

Total snakebite cases admitted to Hi-Tech Medical College from January 2016 to October 2017, which includes two monsoons were enlisted (most of the cases are krait bites

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and few are cobra bites). Out of these, the number of cases undergone imaging studies such as x-ray, USG, Doppler, CT scan, CT angiography and MRI studies were included in study group. The findings were analysed in background of pathophysiology and toxic action of neurotoxic snake venoms.

RESULTS AND ANALYSIS OF THE IMAGIOLOGICAL FINDINGS

Total number of snakebite cases in our study group is 52. Total number of case undergone imaging study = 11 (CT=7, MRI=4, USG=3, Doppler=1, x-ray=2) with overlapping of multiple investigation for few patient. The cases showing positive findings were given bellow.

(I) Four cases undergone brain MRI-
 Out of these, one case undergone MRI study during treatment as the altered sensorium was prolonged for 2 weeks even without any evidence of respiratory failure and blood coagulation test was normal. The MRI findings are as follows (Figure 1). The MRI finding shows bilateral symmetrical T2 hyperintensities in capsuloganglionic area, corona radiate and corpus callosum. These areas show restricted diffusion. It was diagnosed as delayed complications probably due to snakebite-induced leucoencephalopathy⁹ treated with steroid along with other supportive drugs and was recovered fully.

The 2nd case undergone MRI study after 2 months of recovery due to sudden onset of altered sensorium. MRI shows (Figure 3) T2 hyperintensities in bilateral capsuloganglionic and right frontoparietal and left temporal area with evidence of mild restricted diffusion. The CT scan was done 4 days before, but was inconclusive. This case was diagnosed as delayed complication due to ASV-induced immunological reaction¹⁰ and adequately treated with steroids and was recovered.

The 3rd case was done after 3 months of recovery who developed altered sensorium. The MRI finding (Figure 4) shows multiple small hyperintense lesions in bilateral subcortical paraventricular area. Two larger lesions show restricted diffusion. It was diagnosed to be late complication of ASV showing ADEM like symptoms.¹⁰ Accordingly, the patient was treated and recovered.

The 4th case developed vomiting with deteriorated sensorium within a week and then CT scan was done. It shows (Figure 5, 6) intraventricular bleed and petechial haemorrhages in right temporal area. Two days after, again MRI was done, which shows (Figure 2) haemorrhagic infarcts in right temporoparietal and is associated with intraventricular bleed. This is probably due to coagulopathy developed after snakebite, i.e. stroke-like symptoms.¹¹

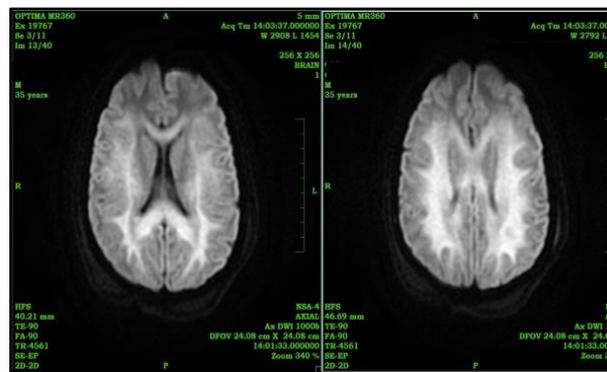


Figure 1. 35 Y/M. T2 Flair Diffuse White Matter Hyperintensities

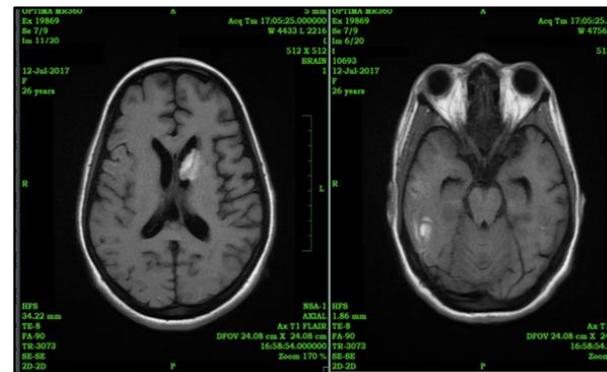


Figure 2. 26 Y/F. T1 Flair Evidence of Intraventricular Bleed Petechial Haemorrhage in Right Temporal Lobe

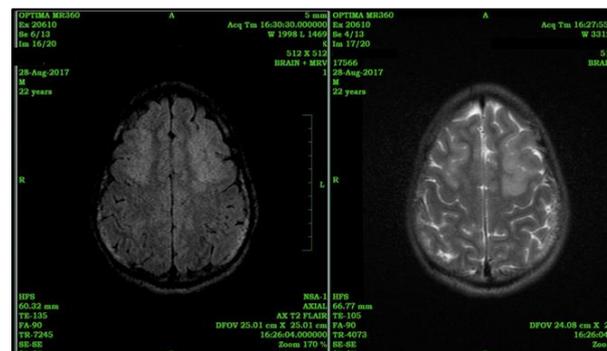


Figure 3. 22 Y/M. T2 Flair and T2WI Bilateral Symmetrical Subcortical Hyperintensities in Bilateral Frontal, Temporal and Parietal Lobes

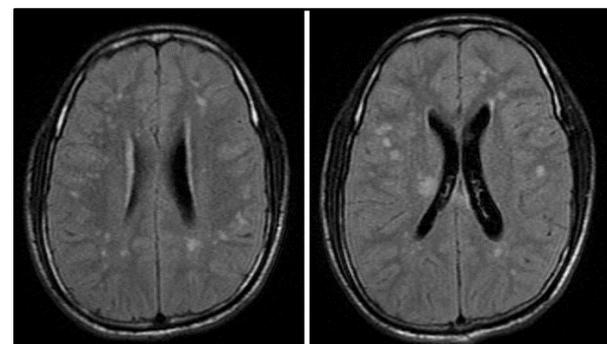


Figure 4. 23 Y/M T2 Flair Multiple Small Hyperintensities in Subcortical and Paraventricular Areas

(II) Seven cases undergone CT Scan-

- After 1 week, developed hemiplegia, CT scan showed intracerebral haematoma (Figure 7) due to coagulopathy.¹¹
- One young patient having tingling sensation throughout the body with history of snakebite 1 month back and shows normal CT scan was normal, the cause could not be found out.
- One old patient developed reeling of head with history of snakebite, 2 month back, the CT scan showed few lacunar infarcts in left

capsuloganglionic area probability due to ischaemic changes not related to snakebite.

- One patient having headache with intermittent vomiting with history of snakebite 3 months back CT scan came was normal.
- Other two cases of CT scan were done before their MRI scan mentioned above.
- One case undergone CT angiogram after Doppler study due to persistent oedema with blackish patches (Figure 8).

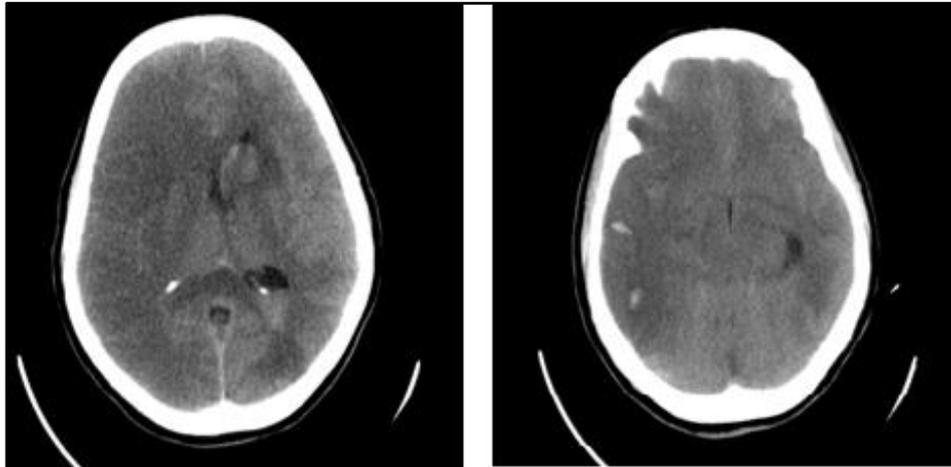


Figure 5 and 6. A 26 Y/F. NCCT Brain. Evidence of Intraventricular Bleed Petechial Haemorrhage in Right Temporal Lobe

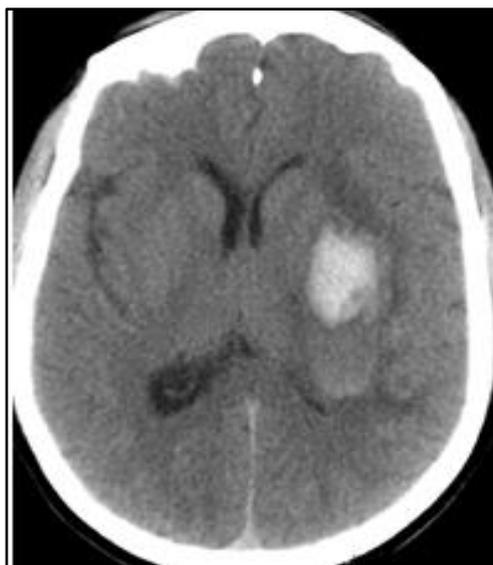


Figure 7. A 38 Y/M. NCCT Brain. Evidence of Intracerebral Haematoma



Figure 8. A 28 Y/M. Normal Angiography of Right Lower Limb (Snakebite Site)

(III) Other imagiological investigations done are x-ray, USG and Doppler and HRUS.

One case was referred for x-ray to rule out osteomyelitis in a badly infected wound developed after snakebite. X-ray shows soft tissue oedema without any evidence of osteomyelitis.

Another case with persisting oedema, patchy black areas around the snakebite site referred for x-ray/USG and colour Doppler study to rule out any local complication or

vascular complications or evidence of osteomyelitis. The findings are diffuse soft tissue oedema detected in HRUS. Doppler study was normal. X-ray shows soft tissue oedema. This case was again undergone CT angiography.

USG for a renal failure case with history of snakebite showed grade-II renal parenchymal change.

Another case undergone HRUS of snakebite site and show mild local swelling.

DISCUSSION

Role of Imaging with Indication- In snakebite cases imaging plays an important role where there is diagnostic dilemma in following situations.

1. When the neurological deficits persist for a longer period even after the patient recovered from respiratory failure.
2. Acute alteration of sensorium and development of neurological symptoms during treatment.
3. Recurrent neurological symptoms after a substantial period of recovery.
4. For unexplained symptoms, which may or may not relate to snakebite symptoms and for other psychological symptoms.
5. Aggravated and non-healing local infections around the snakebite site.
6. Complication due to involvement of other vital organs like kidney.
7. Rare complications with involvement of organs like eye, vascular system, abdomen, musculoskeletal system and cardiac stroke-like situation.

Pathophysiology- Neurotoxicity is a well-known feature of envenoming due to elapids and also in few species of viperidae, i.e. Russell viper and Pit viper. True viperidae group of snake cause haemotoxicity. They can cause secondary complication in different organs when it affects brain, then it cause secondary neurotoxicity.

The neurotoxic effect related to snakebite due to following mechanism.

- (1) Critical illness myopathy-
Acute neuromuscular paralysis of respiratory muscle is the main type of neurotoxicity and is the most important cause of mortality.
- (2) Other acute neurological manifestations.
 - I. Acute symptoms, which are limited to case reports and are not well understood.
 - II. Some acute neurological symptoms, which are due to direct action of toxins.
- (3) Neurological manifestations of non-neurotoxic envenoming effect.
 - I. Cerebral haemorrhage.
 - II. Infarction.
 - III. Hypoxic encephalopathy secondary to respiratory paralysis.
 - IV. Myotoxicity and cardiotoxicity (direct).
- (4) Treatment-induced neurotoxicity.
 - I. Immediate onset.
 - II. Late onset.
- (5) Emotional response to snakebite such as hypotension and shock leading to other organ manifestations.

Neuromuscular Paralysis (Critical Illness Myopathy) with Role of Imaging

The main action of neurotoxic snake venom is at neuromuscular junction. Here, we have discussed mainly the pathophysiological basis of neuromuscular paralysis. Besides this, the immunological basis for antivenom-induced

neurotoxic and neurotoxicity manifestations of non-neurotoxic snake venom also discussed shortly. The role of imaging in above cases are also discussed.

Whole of the nervous system consists of millions of neurons, axons and synapses extends from CNS to the end organs. Acetylcholine plays an important role in all the synapses of peripheral nervous system, preganglionic fibres of autonomous nervous system including postganglionic fibres of parasympathetic system and in some part of the central nervous system.

At presynaptic level, nerve axon terminal is responsible for synthesis, packing, transport and release of neurotransmitter acetylcholine (Ach). The incoming axon potential in presynaptic nerve endings, triggers the opening of voltage gated calcium channel and cause influx of calcium ions. Increased intracellular calcium concentration again triggers a cascade of events leading to the formation of a fusion complex made up of SNARE proteins (soluble N-ethylmaleimide-sensitive factor attachment receptor protein). This receptor protein enables fusion of Ach vesicles to nerve terminal membrane and cause Ach release into synaptic clefts.¹²

From synaptic cleft, the required amount of Ach binds with the nicotinic Ach receptors (nAChRs) in postsynaptic membrane at neuromuscular junction and propagate further action in postsynaptic cell and rest of the amount of released Ach in synaptic cleft undergo degradation by acetylcholinesterase and the end products siphoned back to presynaptic nerve ending for reutilisation. According to the demand of Ach in synaptic cleft, the Ach release is facilitated through nicotinic receptor of preganglionic nerve terminals, which mobilises the Ach vesicles from reserve pool to releasable pool by positive feedback system.¹³ In postsynaptic level, Ach binds to the nicotinic receptor (nAChRs) of postsynaptic membrane. These nAChRs are ligand-gated ion channels, hence their activation by Ach binding leads to influx of sodium and calcium cations accompanied by an end-plate potential, which is propagated along perijunctional zone and muscle membrane and initiate muscle contraction.^{13,14}

Coming to neurotoxic action of common poisonous snake venom is India, they cause two type of actions, i.e. of postsynaptic and presynaptic.

Snake venoms do not contain a homogeneous single toxin, but are complex cocktail of enzymes, polypeptides, non-enzymatic protein nucleotides and other substance, many of which may have different neurotoxic properties.^{15,16} According to the concentration of different component in different type of snake venoms, the degree of action in presynaptic and postsynaptic level varies and accordingly the clinical symptom varies. It varies in different species in same genera even in same species in different geographical area.¹⁷ Many type of venom are known to contain both pre and postsynaptically active toxins. In India, the common poisonous snakes show following toxins.

- (1) Venom of Russell's viper.
 - Presynaptic - PLA2 toxin.
 - Postsynaptic- Dntx-1 (Dobia neurotoxin).

- (2) Venom of krait.
Presynaptic- β -Bungarotoxin (PLA2 action).
Postsynaptic - α -Bungarotoxin.
- (3) Venom of cobra.
Postsynaptic (nAChRs) - α -cobratoxin.

In presynaptic active neurotoxins are mostly β -neurotoxins (phospholipase A2 toxins - PLA2 toxin) binds to the nerve terminals leading to depletion of synaptic Ach vesicle, impaired release of Ach followed by enhanced Ach release and then complete inhibition of NMJ transmission and degeneration of motor nerve terminals.^{18,19,20,21} β -bungarotoxins has predominant PLA-2 enzymatic activity. By 12 hours of envenomation by B-bungarotoxin all muscle fibres were denervated and reinnervation began at 3rd day and takes around 7 days for full recovery in experimental animals.²²

The postsynaptic active neurotoxins mostly the α -toxins, bind to postsynaptic muscle nAChRs. It belongs to group of three finger toxins (3FTXs) classified into three main groups long chain, short chain and non-conventional α -neurotoxins and they act as curare-mimetic. Some toxins, α -cobratoxins (a short chain 3FTs) and non-conventional α -neurotoxins cause a reversible non-depolarising postsynaptic block by competitive binding to muscle nAChRs and also inhibit the presynaptic nAChRs. In this type of toxicity, antivenom may facilitate dissociation of toxins from ACh receptor and accelerate recovery and also show clinical improvement by acetylcholinesterase inhibitor therapy. But, most of the α -neurotoxin, however, bind almost irreversibly to the postsynaptic nAChRs, hence their action not readily reversible by antivenom or AChEIs. These include most of the long chain 3FTXs such as α -bungarotoxins. In these, circumstances needs only respiratory support till complete re-ervation is completed.²³

These patients hardly needs imaging study, but in few instance, chest x-ray or CT thorax done to rule out ARDS. But, in case of secondary hypoxic encephalopathy and in instances of delayed recovery, MRI is needed to know the extent of brain damage.

Other acute neurological manifestation (central effect) with role of imaging.

Besides these, neuromuscular paralysis, several other acute neurological manifestations have been reported, which are likely to be direct neurotoxic effects. The mechanism of many of these acute manifestations are not well understood. These are, drowsiness and loss of brainstem reflexes, altered consciousness and coma had been reported.

Imaging plays an important role to differentiate whether these symptoms are due to direct neurotoxicity of venom in brain or due to infarct/haemorrhage, which are common in viperid bite. In our study, three such cases are encountered.

Other acute symptoms reported are seizures and alternation of smell and taste and neuropathies and

ophthalmopathy. But, the exact mechanism has not been identified.

Here Imaging (CT/MR) is needed to Rule out IC SOL and Other Changes-

Delayed neurological manifestations with role of imaging:-

1. Persistence of neurological deficit developed during acute stage for more than 15 days.
2. Neurological deficits developed at variable time points after recovery. These are due to non-length dependant peripheral type of polyneuropathy. It may mimic GBS or may not. The possible cause could be direct axonal damage by neurotoxins or delayed immune-mediated reaction to toxins or antivenom. Besides polyneuropathy, several cases mimicking, PRES, ADEM, cerebral ischaemia, leucoencephalopathy has been reported. These mostly attributed to immune-mediated antivenom.

In these cases, MR imaging plays an important role. One such type of case has been described in our study.

Other local and systemic complication where imaging helps-

1. Cellulites to exclude osteomyelitis- x-ray.
2. Persistent swelling of limbs to exclude, DVT/collections/osteomyelitis = Doppler/USG/x-ray/MRI.
3. Atrophy of the limb where snakebite has occurred due to myotoxic effect to rule out other causes by USG and MRI.
4. In badly infected limb following snakebite- HRUS, Doppler and CT angiography is indicated to exclude the arterial involvement or any collection.
5. Loculated intra-abdominal haematoma needs abdominal USG or CT.
6. In early stage of osteomyelitis, which could not be detected by x-ray can be detected by MRI.
7. Renal failure cases needs repeated USG.

CONCLUSION

Imaging has limited roles in snakebite cases, but plays an important role in cases with acute and delayed central neurological manifestation of neurotoxic envenomation, coagulopathy effect in brain, abdomen and other organs, local complications and systemic complications for diagnosis and further treatment.

Need further studies for better understanding of unexplained symptoms and mode of action of different toxins in snake venom and their variable action in different geographical areas. Reporting of all imaging findings in different snakebite cases can help better utilisation of imaging system.

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