Snakebite, Antivenom and Mitochondrial Toxicity

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Abstract

Background: Snake bites are common in underdeveloped countries and produces generally cardiac, renal and neuromuscular complications. Common side effect of antivenom is anaphylaxis. Snake poison is the most complex natural poison which acts on the victim by the multiple components present in it. Apart from supportive treatment polyvalent antivenom is used in treatment. Neither the snake venom nor the antivenom is reported to have mitochondrial toxicity so far in literature. **Subject and Methods:** A 10-year-old male child presented with cardiovascular collapse following snake bite and treated with polyvalent antivenom. Following a brief period of recovery, patient presented with features of acute mitochondrial encephalopathy which was confirmed by T2 changes and lactate peak in MR spectroscopy. Child made complete recovery with mitochondrial cocktail. Investigation for mitochondrial Cytopathy with muscle biopsy was normal. However, mitochondrial genetics for primary mitochondrial disease was not done. **Discussion and Conclusion**: It is possible that some of the substances present in the snake venom, antivenom might have mitochondrial toxicity and this should be considered as a possibility when a second encephalopathy occurs following treatment for snakebite.

Keywords: Mitochondrial encephalopathy, Snake bite, Antivenom

Introduction

Poisonous snakes in India belong to the family of Elapidae which includes Cobra, Krait and Mambas and Viperidae which includes the Russell viper, Saw scaled Viper etc. and the sea snakes. Only about 50-70% of bites cause systemic manifestations and the rest are dry bites (34%)^[1]. Snake bite is common in Africa, Asia and Latin America and there are approximately 20,000 deaths and 4,21,000 envenomings worldwide per year. The venom causes damage by cytotoxic substances which cause local swelling and tissue damage, haemorrhagins which disturb the integrity of blood vessels, and components which lead to incoagulable state of the blood, neurotoxins and myotoxins^[2]. Clinical features consists of neuroparalysis and bleeding tendency (hemotoxic/ vasculotoxic), cardiovascular collapse apart from local pain and tissue damage, swelling, blistering, bleeding, and necrosis at the bite site and acute renal failure . Snake venoms are recognized as the most complex of all natural poisons containing a complex cocktail of enzymes, proteins, polypeptides, nucleotides etc. The named toxins are the following. Alpha-cobratoxin, Cobrotoxin, Cardiotoxin, Toxin Alpha, Bungarotoxin, Beta-Bungarotoxin, Kappa Bungarotoxin, Candoxin, Daboia Neurotoxin-1, Viperotoxin-F, Dendrotoxins, Fasciculins, Muscarinic Toxins, Calciseptine, Crotoxin and Mojave Toxin. The mechanisms of the action of these toxins are not well understood but they can produce reversible and irreversible pre and post synaptic neuromuscular junction blockade as well as indirect effects secondary to cardiovascular complications.

Treatment consists of use of univalent or polyvalent antivenom which binds, extracts and eliminates toxins from the body. Hemostasis and cardiovascular function restoration, artificial ventilation and use of anticholinesterase drugs like Edrophonium, Tetanus toxoid as well as antibiotics are used based on the situation. Before reaching the hospital, the affected part should be immobilized with a makeshift splint or sling or crepe bandage to prevent absorption. Role of tourniquet is controversial ^[3-5].

Antivenin is derived by immunizing Horses or Sheep with snake venom in gradually increasing doses until a high titer of immunity is achieved. This serum is then refined to produce the antivenom. Indian antivenoms are polyvalent and effective against Russell's viper, Spectacled cobra, common Krait and saw scaled viper. The potency of the antivenom is 0.6 mg/ ml and 10 ml vial can neutralize upto 6 mg of cobra venom but unfortunately a single bite can inject as much as 742 mg of venom. This is not useful for the local necrotic type of envenomation. The most common complication is anaphylaxis ^[4].

There are large number of proteins in the snake venom which differ based on their biological targets and pharmacological effects. They are both enzymatic and non-enzymatic. They are grouped as follows 1) Serine proteinase inhibitors which includes proteinase inhibitors and dendrotoxins, 2) Three-finger toxins like neurotoxins and cardiotoxins, 3) Sarafatoxins, 4) Lectins, 5) Nerve growth factors, 6) Bradykinin-potentiating peptides, 7) Atrial natriuretic peptides 8) Helveprins/CRISP and 9) Disintegrins ^[6].

Case Report

10-year-old male child from Vellore district in Tamilnadu, South India was admitted on January 13th 2014 with following history. He was normal and sleeping when his mother left for shopping

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that morning. When she came back child was unconscious and frothing from mouth. He was taken to a local hospital where bite-marks were identified by the medical officer as snake bite and treated accordingly with polyvalent antivenom. Seven days later he was showing signs of improvement and discharged with mild right sided weakness. 3 days after discharge from the primary care hospital, he had a seizure following which he steadily deteriorated and at the time of admission to us 4 days after the seizure child was not communicating, had intermittent oculogyric spasms, his neck was turned to the left and back, he was in opisthotonus with trunk twisted to left, left upper limb internally rotated, left lower limb extended, left ankle plantar flexed and left striatal toe. Right leg was flexed at hip and knee and inverted at ankle. Toes were in dystonic posture. His right upper limb was normal. He appeared to recognize parents [Figure 1]. He was investigated with cerebrospinal fluid tests for evidence of infection including IgM antibody for Japanese encephalitis, herpes virus antibody. liver function tests, renal function tests and routine examinations were normal. Serum Ammonia was 39 micromol/liter and lactate 12.3 mg/dl. Blood pH 7.49, pCO₂ 33.7, PO, 78.6. Tandem Mass Spectroscopy for inborn errors of metabolism showed elevated propionyl carnitine. Urine screening for abnormal metabolites negative. Urine for organic acids showed mild elevation of oxalic acid, homovalinic acid, and glycolic acid. Magnetic resonance imaging of brain revealed Bilateral symmetrical T2 prolongation, FLAIR hyper intensity noted involving caudate, putamen, globus pallidi with T1 shortening involving globus pallidi externa. No diffusion restriction was seen except mild hyper intensity of the Parietal cortical regions on both sides. Subtle hyper intensity of bilateral thalami also noted on T2W, PD images. MRS showed lactate peak suggestive of mitochondrial encephalopathy. Spine screening was normal. The MRI is typical in the following case showing.

1. Lactate peak in MRS

2. The changes are bilateral and symmetrical.

3. In demyelination which involves the basal ganglia region, the lesions are always almost asymmetrical. They show the open ring pattern of enhancement with the opened part towards the cortex.



Figure 1. Dystonic posture with ophistotonus.



Figure 2. A FLAIR hyper intensity is noted involving caudate, putamen, globus pallidi with T1 shortening involving globus pallidi externa. **B**. hyper intensity of bilateral caudate, putamen, globus pallidi and thalami is also noted on T2W images. **C**. mild hyperintensity of the Parietal cortical regions on both sides in the diffusion sequences **D**. MRS shows lactate peak and suggestive of mitochondrial encephalopathy.

4. The white mater being more myelinated than the grey matter, the internal capsule shows maximum involvement in demyelination. In our patient, the white matter is spared and there is no open ring enhancement and the changes are symmetrical. [Figure 2].

Possibility of primary mitochondrial abnormality unrelated to snakebite was also suspected and muscle biopsy was done. Muscle fibers showed preserved architecture Succinate dehydrogenase (SDH), Niccotinamide Adenine dinucleotide tetrazolium reductase (NADH TR), Modified Gomoris trichrome staining (MGT), Mitochondrial Acetyltransferases Type B (MAT -B) and Succinyl dehydrogenase -Cytochrome oxidase (SDH -COX) staining were normal. ATPase 9.4 and 4.6 showed mild type 2 atrophy. This clinical and radiological picture after excluding other causes suggested a mitochondrial encephalopathy as evidenced by signal changes and lactate peak in MR spectroscopy. Patient was put on complete mitochondrial cocktail and symptomatic medication. Patient steadily improved and at the time of last follow up in June 2015 patient has no dystonias and fully independent with no symptomatic drugs [Figure 3]. His parents reported minor behavioral problems like occasional anger out bursts. His MRI was repeated which showed very minimal residual changes.

Discussion

Our patient was diagnosed as a case of snake bite with cardiovascular collapse at the regional government institution based on bite-marks identified by the medical officer and features of cardiovascular collapse and history of bite confirmed by the child later. The type of snake could not be identified. He was treated by the Indian polyvalent antivenom and recovered over a period of one week. Following brief period of recovery, child deteriorated with severe generalized involuntary movements. Child was not on any antipsychotics and imaging features were suggestive of mitochondrial encephalopathy. He was investigated for primary mitochondrial disease with muscle biopsy, serum lactate and ammonia levels. However, complete mitochondrial genetics could not be done due to financial constraints. He was treated with complete mitochondrial cocktail consisting of Co-enzyme Q10 5 mg/kg/day, Levo



Figure 3. Patient has no dystonias and fully independent after treatment.

carnitine 66 mg/kg, Vitamin B1 100 mg/day, Vitamin E 400 mg/day, Riboflavin 5 mg/kg/day Vitamin C 500 mg/day, Alpha lipoic acid 100 mg/day, Vitamin B6 40 mg/day, Vitamin K 10 mg/day and showed complete clinical and radiological recovery. Intravenous fluids were given based on hydration level using glucose saline and Ringer lactate. The patient was treated as in patient for a period of 3 weeks ^[7-9].

The clinical, radiological features along with complete recovery following mitochondrial cocktail suggests the possibility of a secondary mitochondrial damage due to some exogenous agent. It could be the snake venom or the antivenom. The well-known mitochondrial poisons are anticancer drugs, antiviral drugs, carbon monoxide, chloramphenicol, Sodium Valproate, Phenobarbitone, Electron transport inhibitors like Rotenone, Antimycin, Cyanide, Malonate (succinate dehydrogenase inhibitor), Uncoupling agents like 2,4-Dinitrophenol (DNP), Carbonyl cyanide p-¹trifluoromethoxy].-phenyl-hydrazone (FCCP) and Oligomycin (inhibitor of oxidative phosphorylation)^[1,7].

Conclusion

Patient developed the encephalopathy following a period of recovery ^{[9].} Therefore it is less likely to be the direct effect of either the envenomation or antivenom. However, it is likely that snake venom, the most complex of all natural poisons might

have effect on mitochondrial energy metabolism. We could not get any reference for the same in the literature. Hence possibility of secondary mitochondrial damage following either snakebite or antivenom therapy with complete recovery is postulated. This case is being reported as a possible case of delayed mitochondrial damage resulting in encephalopathy secondary to unknown snake envenomation. It is possible that some of the substances present in the snake venom might have mitochondrial toxicity and this should be considered as a possibility when a second encephalopathy occurs following treatment for snakebite.

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