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Acute Fatal Stroke Associated with Honeybee Sting

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ABSTRACT

The venom toxins of honeybee cause anaphylactic allergic reactions and/or any type of stroke. Hemorrhagic strokes are more severe than the ischemic strokes. Diverse pathophysiological mechanisms have been postulated for occurrence of these strokes. We discuss here mechanism of acute fatal hemorrhagic and ischemic stroke in a middle age woman, stung by the honeybee on her right arm and who clinically manifested loss of consciousness and tonic clonic seizure, within 3-4 hours followed by hemiparesis. The MRI revealed brain lesions of multiple infarctions with hemorrhagic transformation, subdural (SDH) and subarachnoid (SAH) hemorrhages. This appears to be the first report, wherein a patient had entire spectrum of stroke (infarcts, subarachnoid and subdural hemorrhages), after a single inciting event of bee sting.

Introduction

Stroke is the second most common cause of death and major cause of disability worldwide. Apart from anaphylactic allergic reactions, the sting venom of honeybee (*Apis mellifera*, *Order- Hymenoptera)*, can cause hemorrhagic as well as ischemic strokes. These neurological deficits are produced by the contents of venom toxins directly or through the anaphylactic shock or pain induced catecholamines surge. The venom contains biologically active enzymes, amines and proteins. These substances directly or indirectly cause multitude of medical complications due to local, regional or systemic allergic reactions[1]. The local reactions cause local edema and swelling with symptoms that usually resolve within 24 hours. Contrarily, regional and systemic reactions cause significant morbidity and mortality. These reactions have protean manifestations ranging from anaphylaxis, hypotension, rhabdomyolysis, seizures, disseminated intravascular coagulation (DIC) to intracranial hemorrhages and cerebral infarctions, leading to the causation of stroke through different mechanisms[2]. Only a few cases are reported in the literature with hemorrhagic stroke as an initial complication. We report here, a case of progressive multiple infarcts with subdural and subarachnoid hemorrhages, occurring within 3-4 hours of bee sting in a middle age woman, who manifested tonic-clonic seizures followed by hemiparesis.

Case Report

A 41-year-old previously healthy woman, while working in her field, was bitten by a honeybee with a single sting over her right arm. She developed right arm and forearm swelling with pain. She was taken to a nearby hospital, where she was managed with intravenous antihistaminic and steroids. After 3 hours of sting, she developed a generalized tonic clonic seizure episode followed by left sided hemiparesis, dysarthria and became unconscious. She was started with antiepileptics. On the

second day, she was taken to another hospital, her brain magnetic resonance imaging (MRI) showed infarcts with hemorrhagic transformation in the left temporal and frontoparietal region with SAH along sulci of left cerebral hemisphere and SDH along left fronto-temporo-parietal region (*Figure-1A-E*). Her total leukocyte count was 9360/cumm, Hemoglobin 12.5 g/dL and platelet count 2x10^5 /uL. Her liver and kidney functions were normal. There was no history of fever, dyspnea or vomiting. She was non-smoker and non-alcoholic. Past medical and surgical history was insignificant. Family history was negative for strokes and seizures.

On the fourth day of the sting, she was referred to our institute. At the time of presentation in emergency, her vital signs were: Glasgow coma score 7/15 [E2 V2M3], blood pressure 120/76 mmHg, afebrile and respiratory rate 22/min. While examining the patient, she had another episode of seizure. She was managed aggressively and shifted to ICU. Seizures were controlled by antiepileptics. Her computed tomography (CT) confirmed the cerebral infarct on the left fronto-parietal and temporal regions with subdural collection. Patient had dyspnea and was intubated. Within next 2-3 hours, her blood pressure dropped to 100/60 mmHg and had fever (101.5º F). Chest was bilaterally normal on auscultation. Pupils were normal in size but sluggishly reactive. Planters were extensor on right and flexor on left side. No bleeding was noted from any site. Her ECG, carotid doppler and Transthoracic echocardiography were normal. Her total leukocyte counts were 10200/cumm, Hemoglobin 12.4 g/dL and platelet count 2.1 x10^5 / uL. Although renal function tests were normal yet there was proteinuria. Serum sodium was 148 mEq/l and potassium 4.0 mEq/l. Serum specific honeybee IgE antibodies could not be evaluated due to lack of facilities.

Her serial investigations on the next day i.e. 5th day of sting, showed deranged liver function tests (Total serum bilirubin 1.8 mg/dL with direct bilirubin 0.6 mg/dL and indirect bilirubin 1.2mg/dL, Aspartate aminotransferase (AST) 82 U/L, Alanine aminotransferase (ALT) 49 U/L, Alkaline phosphatase 196 U/L and serum albumin 2.9 gm/dL). Serum sodium increased to 173 mEq/l while potassium decreased to 2.9 mEq/l. Serum calcium was mildly low 8.1 mg/dL while serum magnesium was slightly raised 2.8 mg/dL. Electrolytes were corrected to some extent. Her coagulation profile showed prolonged Activated partial thromboplastin time (APTT) as 44.2 seconds and prothrombin time (PT) as 16.7 seconds, whereas international normalized ratio (INR) was 1.4. Her platelet counts further decreased to 1.6 x10^5 /uL. Her fibrinogen degradation products (FDP) was also elevated (>10 but <20 ug/ml) suggestive of disseminated intravascular coagulation (DIC). She did not improve on antiepileptics, antibiotics, mannitol and adequate hydration. MRI Brain was followed up after 2 days and it showed increase in the size and number of infarcts (*Figure-1F-J*). Magnetic Resonance angiography and venography of brain revealed normal course, caliber, branching and flow related enhancement of intra cerebral portion of both internal carotid arteries. On the 7th day of sting, she died of shock as a result of hemorrhagic stroke due to DIC.

Discussion

After bee stings, there is an increase in cytokines mainly the interleukins such as IL-1, IL-6, IL-8 and tumor necrosis

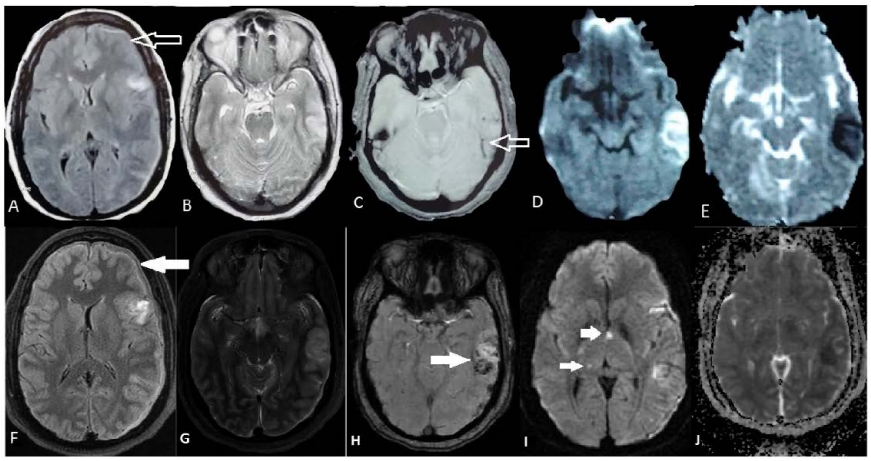

Figure 1 (A-E): shows multiple sequences [FLAIR, T2, SWI and DWI] of MRI of Brain showing SDH along left fronto-temporo-parietal region [indicated by arrow in *A*] with SAH along sulci of left cerebral hemisphere [indicated by arrow in *C*] and infarcts with hemorrhagic transformation in the left temporal and frontoparietal region [*C and D*]. *Figure 1 (F-J):* shows the follow up MRI showing similar sequences with increase in the size and extent of SDH [indicated by solid arrow in *F*] and increase in infarcts with appearance of new lesions in bilateral thalamus [indicated by solid arrow in *I*] and increase in the size of hemorrhagic transformation [indicated by solid arrow in *H*].
SWI= Susceptibility Weighted Imaging, DWI= Diffusion Weighted Imaging, FLAIR= Fluid Attenuation Inversion Recovery

factor (TNF)[3], which trigger adverse effects on the skeletal muscles, bone marrow, hepatic and renal functions, cardiovascular, central nervous and immune systems. In our case, acute fatal ischemic and hemorrhagic stroke occurred.

The bee venom induced neurologic manifestations include stroke, epilepsy, polyradiculopathy, cranial nerve palsies and cavernous sinus thrombosis. The reported time interval between envenomation and the stroke ranged from 15 minutes to 4 days with a median of 16 hours[2]. Our patient had onset of stroke 3-4 hours after envenomation. Since no hypotension or allergic reaction was noted in our case and the patient was stung only on her hand, it is unlikely that the stroke was related to the retrograde intense activation of the superior cervical sympathetic ganglion or anaphylactic shock or hypotension.

Hemorrhage can be induced by the honeybee venom components, especially melittin which interfere with the complement cleavage and bradykinin (BK) release. The latter inhibits the role of thrombin and platelet activation in clotting and induces nitric oxide production in the endothelial cells which further inhibits the adhesion of thrombocytes to the endothelia. Both mechanisms are directly or indirectly associated with the coagulation, thrombolysis, hemolysis and smooth muscle tone. The membrane bound monomers of melittin produce transient openings through which internal bleeding occurs[1]. In addition to Melittin, the bee venom also contains apamin, phospholipase A2 (PLA2), mast cell degranulation peptide, hyaluronidase, histamine, dopamine and hemolysins that cause toxic and hemolytic effects. The most fatal part of the bee venom is PLA2. However, the joint action of both melittin and PLA2 has more pronounced hemolytic property which induces profuse and sudden bleeding resulting in hemorrhagic stroke. Hyaluronidase catalyzes hyaluronic acid degradation. Hyaluronidase also exhibits strong anticoagulant activity[1]. A clinical survey showed that serum hyaluronidase level was increased a few days after the SAH[4]. This shows that hyaluronidase has some role to play in the development of SAH, which needs further confirmation.

In our case, there were prolonged APTT and PT. *Petroianu et al* reported that PLA2 in the venom is known to cause coagulation abnormalities. They reported that in human plasma, several parameters of coagulation were affected due to an increase in concentration of PLA2. The study found correlation between high concentration of PLA2 in human plasma and prolonged PT, APTT and antithrombin III[5]. Additionally, the bee venom also contains thromboxane and leukotrienes, which contribute in vasoconstriction resulting in cerebral infarction. Mast cell mediators also induces hemorrhagic reactions. Cytoplasmic granules contain vasoactive substances (tumor necrosis factor α, histamine, heparin and proteases). Once these mediators are released, mast cells act on the basal membrane and induce brain edema, prolonged extravasation, damage to the blood-brain barrier and causes hemorrhage[6]. The outcome, following the stroke depend on the nature of lesion, like location and size of the infarct/hemorrhage, hematoma expansion, edema formation and intraventricular hemorrhage[7]. Thus, in our case, the concerted action of the melittin, PLA2, hyaluronidase and mast cell mediators produced multiple brain infarctions with hemorrhagic transformation and SDH as well as SAH that resulted in hemorrhagic stroke due to DIC, occurred by coagulation cascade inhibition, thrombus formation and vasoconstriction.

Hepatocellular dysfunction also occurs due to adverse reactions of the bee venom content[3]. Our patient had elevated serum level of bilirubin (total, indirect as well as direct), ALT, AST and alkaline phosphatase. The bee venom activates mast cells that trigger the development of prothrombotic state[3]. Thereby, it is possible that the venom induced reversible prothrombotic state was responsible for the liver cells injury, in our case. Consequently, hepatic dysfunction also contributed in the loss of consciousness which further progressed to deep coma.

In the literature, *Dikici et al* reported a case of a man in his 40s, presented with generalized tonic clonic seizure and loss of consciousness after an hour of wild bee bite on the anterior abdomen. His cranial computed tomography revealed SAH. The patient was treated for a month and discharged in a vegetative state[8]. Likewise, *Kozak et al* also reported a case of a man in his 60s, presented with tonic clonic convulsions and loss of consciousness following bee sting. His CT scan showed widespread SAH between cerebral sulcus, in the ventricular system and in the cisterns. The patient died during treatment on the 4th day of sting[9].

The generalized tonic clonic seizures are related to the state of hypernatremia due to osmo-regularity mechanism in muscle cells. Moreover, studies performed on the mice, injected with PLA2 including bee venom suggested that these substances bind to the related receptors on the specific neuronal sites, leading to the development of seizures. These seizures are reported to be refractory to the blockage of calcium and potassium channels or NMDA and GABA receptors[10]. It is noteworthy that serum calcium and potassium were low in our case.

Treatment regimen should include corticoids, antihistaminic and antiepileptic drugs in diminishing the allergic reactions and controlling the seizures, respectively. In severe complications, such as brain infarctions, intracranial hemorrhages and strokes, rapid recognition and rationale approach is desirable.

Conclusion

Bee venom related neurologic events like stroke, are very rare. In such cases, if the symptoms are maximal at the onset followed by generalized tonic clonic seizures and loss of consciousness, there is likelihood of a fatal hemorrhagic stroke due to the SAH and cerebral infarctions. Such cases should be managed diligently, without any further delay.

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Ethics Statement and Statement of Informed Consent: Written permission was obtained from the patient's kin (since the patient died) in compliance with any laws regarding patient authorizations relating to the use or disclosure of protected health information of the jurisdiction to which the patient and the physician are subjected to. **No experimental investigation of human subjects was done in this study.**

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