HYMENOPTERA STINGS AND THE ACUTE KIDNEY INJURY

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ABSTRACT

Hymenoptera stings are a health concern. Apidae (bees), Vespidae (hornets, yellow jackets and wasps) and Formicidae (ants) are medically-important stinging insects under the order Hymenoptera. Clinical features from simple skin manifestations to severe and fatal organ injury are due to the hypersensitivity reactions and/or the toxic effects of the venom inoculated. Here we discuss on Hymenoptera stings involving apids (honey bees) and vespids (wasps, hornets and yellow jackets) and their effect on renal function and associated morphological changes in the kidney. Despite the differences in venom composition and quantity released per sting in two insect groups, both lead to similar medical consequences, such as localised normal allergic reactions, mild to severe anaphylaxis and shock and multiple organ and tissue injury leading to multiple organ failure. Acute kidney injury (AKI) is one of the unusual complications of Hymenoptera stings and has the basis of both immune-mediated and toxic effects. Evidence has proven that supportive therapy along with the standard medication is very efficient in completely restoring the kidney function without any recurrence.

Keywords: Acute kidney injury, allergic reactions, Hymenoptera stings, renal replacement therapy, toxic reactions, venom.

INTRODUCTION

Animals that produce toxins are classified as either venomous or poisonous. Venomous animals are capable of producing and delivering the toxin during a stinging or biting act whereas poisonous animals are those whose tissues, either in whole or in part are toxic.[1] About 75% of the world's animal species are arthropods, some of which have appreciable interaction with humans and are capable of causing significant medical problems.[2] Approximately 5 million snake bites, scorpion stings and anaphylactic reactions to insect stings occur worldwide annually, causing over 100,000 deaths each year, most of which happen in the tropics.[3] Hymenopterous insects, snakes and spiders are the three animal groups most often responsible for human deaths attributable to venomous animals.[1] The stinging insects are members of the order Hymenoptera of the class Insecta, of which the three medically important groups belong to families of Apidae (bees), Vespidae (wasps, hornets and yellow jackets) and Formicidae (ants).[4] Globally 13,671 people are exposed to Hymenoptera stings.[5] In England and Wales, about 10 people die each year from Hymenoptera sting anaphylaxis, in Australia 2-3 per year and in United States 40-50 per year.[6] In Nepal, the number of inpatient morbidity due to contact with Hymenoptera in the year 2010/2011 was 5.[7]

The sting becomes clinically significant if the patient has an allergy to Hymenoptera venom or if the patient is exposed to a large quantity of the venom due to mass/multiple stings. Most deaths related to Hymenoptera stings are the result of immediate hypersensitivity reactions causing anaphylaxis. However, death may also occur from severe local reactions, particularly if involving the airways with subsequent respiratory obstruction. Massive envenomation during swarm attacks can likewise cause death in non-allergic individuals.[4] A wide range of clinical sequelae involving multiple organ systems is observed during massive envenomation.[8-12] As a highly vascularised and excretory organ, the kidney is particularly vulnerable to Hymenoptera toxins.[3] In this review, we restrict our discussion to the immune-mediated and toxic effect of the vespid and the apid venom, with an emphasis on renal involvement.

APID VERSUS VESPID VENOM

Apid Venom

Honeybee venom is similar among the different Apis species with minor variations in component quantities.[13] Melittin is a major bee venom component (50% of dry weight) and the main pain-inducing compound. It consists of 26 amino acid residues[14] with only 28% of patients having specific immunoglobulin E (IgE) antibodies against it.[15] Melittin functions by altering the membrane integrity. The most important allergen in honeybee venom is phospholipase A_2 (PLA_2), which is a high molecular weight glycoprotein with 134 amino acid residues. The enzyme acts as a cytotoxin and an indirect cytolysin as it works in concert with melittin.[13,16] These two components are responsible for red-cell lysis. Once melittin has disrupted the membrane, PLA_2 cleaves bonds in the fatty acid portion of the membrane lipid bilayer. Hyaluronidase (1%-2%) is a secondary allergen and shares a 50% sequence identity with vespid venom allergen. It also disrupts the hyaluronic acid connective tissue matrix and allows the other venom components to infiltrate the tissues. Peptide 401, a mast cell degranulating protein (2%) causes mast cells to break down releasing histamine. Histamine reaction from honeybee envenomation is due to endogenous release initiated by other venom factors, as histamine is only a minor portion of bee venom.[13] However, in mass envenomations the venom histamine is sufficient enough to produce cardiovascular changes.[17] Additional bioactive molecules include acid phosphatase, apamin (a neurotoxic peptide), Api m 6 (an allergenic peptide of molecular weight 7.9kDa), dopamine and norepinephrine.[13,18] Bumblebee venom contains PLA_2, protease, hyaluronidase, acid phosphatase and several other proteins not found in honeybee venom.[19]

Vespid Venom

Vespid venoms are more variable in their composition among the species, different to that of bee venom. The important allergens in vespid venoms are phospholipases, hyaluronidase and antigen 5, with antigen 5 being the major allergen in all vespid venom.[2,20] The phospholipases (PL) characterised in vespid venoms are PLA_1, PLA_2 and PLB.[21] Vespid PLA_2 presents high haemolytic activities whereas PLA_1 is generally associated with allergic and inflammatory processes and also possesses mild to severe haemolysis. However, the potency of vespid phopholipases is variable among the species,[22,23] probably due to the greater taxonomic diversity of the vespids.[13] PLB from vespids not only have enzymatic activity but also have haemolytic activity and cardiotoxicity.[21] Vespid venom also contains active amines such as serotonin, histamine, tyramine and catecholamines. Peptides such as wasp kinins and mastoparans are unique to vespid venoms. Wasp kinins are of interest because two kinins, bradykinin and lysyl-bradykinin, occur in humans, and are generated and act locally in humans but are not stored as in venom. They are potent pain producers and increase vascular permeability. Mastoparan, a cationic tetradecapeptide discovered in wasp venom in a screening test for mast cell degranulating agents, is a major component of vespid venoms.[24,25] Besides mast cell degranulation, they are the potent stimulant of PLA_2 of both venom and victims. Mastoparans bind to phospholipids and facilitate the PLA_2-catalysed release of arachidonic acid, the precursor of prostaglandin and leukotrienes, which are mediators of adverse reactions associated with immediate hypersensitivity.[24] Mastoparan peptides of different vespid origins display haemolytic and cytotoxic activities of varying degrees, which are attributable to amphipathicity that promotes binding to membrane phospholipids.[24,26]

VENOM DOSE PER STING AND LETHALITY

Hymenoptera venom contains both species-specific components and shared components, hyaluronidase and phospholipase being the most commonly shared enzymes.[16,27,28] The amount of venom released per sting also varies among the species and even within the same species.[29] Bee stings release an

average of 50 μg up to 140 μg of venom per sting. Bumblebees release 10-31 μg of venom per sting. Vespids, in contrast to apids, inject less quantity of venom per sting: *Vespula*, *Dolichovespula* and *Polistes* stings release 1.7—3.1 μg, 2.4—5.0 μg and 4.2—17 μg of venom protein respectively.[16] Due to the variation in the composition and the quantity of the released venom, the lethal dose (LD_{50}) of venom differs amongst the insects. Renal failure or death may occur in the range of 20-200 vespid stings and 150-1000+ apid stings. The human LD_{50} for honeybee stings has been estimated to be between 500-1200 stings. Vespid venom has more deleterious effects than that of the apid venom. Mammalian toxicity tests on mice revealed that honeybee venom LD_{50} (3 mg/kg) is about equivalent to that of the larger hornet (*Vespa* spp), and three-fold less toxic than that of yellow jacket wasp (*Vespula* spp) venom.[13]

EFFECTS OF VENOM

The venom intoxication has variable effects in individuals depending upon the sensitivity of the person towards the venom and the amount of venom injected into the body. The reactions to vespid stings have been categorised as normal local reactions, large local reactions, graded systemic reactions,[27] systemic toxic reactions[12,30] and unusual reactions.[31,32] The most common clinical pattern of the Hymenoptera stings are the local reactions that resolve within a few hours or large local reactions that last longer than 24 hours, or the systemic reactions grade I—IV.[33,34] Both local and large local reactions are immunoglobulin G (IgG)-mediated type IV hypersensitivity whereas systemic reactions are immunoglobulin E (IgE)-mediated type I hypersensitivity.[27] The unusual delayed reactions are IgG and immunoglobulin M (IgM)-mediated type III hypersensitivity reactions, and includes vasculitis, central nervous system signs and symptoms such as seizures, peripheral neuropathy or radiculopathy, haemolysis, rhabdomyolysis and acute renal failure (ARF).[35] Toxic reactions are attributable to direct or indirect (e.g. immune-complex mediated tissue injury)[36] toxicity of venom, the effect of which might be localised or systemic.[36,37] Most deaths related to Hymenoptera stings are due to the immediate hypersensitivity reactions causing anaphylaxis. Such local reactions and anaphylaxis are not dose-dependent or related to number of stings. However, in non-allergic persons, massive envenomation can cause death, mainly due to the toxic reactions of the venom which are independent of immune mechanisms and are venom-volume dependent.[4] The sting reactions, allergic and/or toxic, affect multiple organs with results varying from a typical dermatologic expression to multiple organ failure.[8-12]

RENAL EFFECTS OF HYMENOPTERA VENOM

Acquired kidney injuries are generally induced by immunological, metabolic, haemodynamic, ischaemic and toxic assaults.[38] The term acute kidney injury (AKI), previously referred as acute renal failure (ARF), represents the entire spectrum of acute renal dysfunction from its earliest and mildest form to the need of renal replacement therapy.[39] The term defines either an abrupt increase in serum creatinine (to denote a reduction in glomerular filtration rate (GFR)) or an abrupt decline in urine output.[40] Hymenoptera envenomation significantly contributes towards AKI via haemodynamic alterations, ischaemic assaults, direct toxicity of venom and immunological mechanisms, which can be grouped under two categories i) immune-mediated effects and ii) toxic effects. The review of literature on AKI following Hymenoptera envenomation enlists the following different pathological findings: acute tubular necrosis (ATN), acute allergic interstitial nephritis (AIN), and acute cortical necrosis (ACN). Other renal changes documented are distal renal tubular acidosis (dRTA), proximal renal tubular acidosis (pRTA) and nephrotic syndrome (NS).

Animal studies with bee venom have demonstrated early and significant reduction in GFR and renal blood flow (RBF) which was more pronounced in cortical region than in medulla. The striking decrease in RBF caused renal ischaemia which ultimately led to the glomerular tuft retraction and mild tubular injury observed in early renal histology, which evolved to frank tubular injury after 24 hours. Grisotto et al.[17] proposed that various venom components such as melittin, PLA_2 and histamine are responsible for bee venom-induced RBF decrease through various mechanisms such as vascular endothelium damage,[41] vasoconstriction,[42] smooth muscle cell contraction,[43] increased renal renin secretion,[44] catecholamines[45] and arachidonic acid release,[46] and enhanced thromboxane B_2 production.[47] Grisotto et al.[17] had shown that bee venom produced clear dose-dependent proximal tubule (PT) toxicity and that the venom may enhance hypoxia/reperfusion injury.

Pigments (myoglobin, haemoglobin or both) are responsible for indirect venom toxicity. Three major underlying mechanisms are i) renal vasoconstriction/hypoperfusion due to fluid third

spacing during myolysis causing intravascular volume depletion or activation of endotoxin-cytokine cascade eliciting renal vasoconstriction, or scavenging nitric oxide (NO) by haemproteins, which is an important endogenous vasodilator, ii) intraluminal cast formation, and iii) haem-mediated proximal tubular toxicity.[48] Decreased GFR due to renal vasoconstriction and volume depletion, both decreases the clearance of haemprotein and increases intraluminal myohaemoglobin concentration favouring cast formation and tubular obstruction, which in turn causes luminal stasis allowing more time for proximal tubular haem reabsorption. The accumulated haemprotein confers tubular toxicity leading to necrosis and ultimately filtration failure. The haemprotein-induced kidney injury are due to i) intense renal vasoconstriction causing ischaemic tubular injury and ATP depletion via haemodynamic (in the setting of volume depletion) and non-haemodynamic (ischaemic interaction directly at the proximal tubular cell level) mechanisms, ii) direct sensitisation by endocytosed haemprotein of tubular cells to ischaemia-triggered membrane injury via PLA_2 attack, and iii) haem iron-induced oxidative stress via hydroxyl radical formation by accumulated intrarenal haem iron leading to oxidant renal damage. Besides haem-protein, other factors produced during rhabdomyolysis and haemolysis such as hyperphosphataemia and hyperuricaemia potentiates ischaemic and nephrotoxic renal damage. Release of tissue thromboplastin in rhabdomyolysis triggers disseminated intravascular coagulation (DIC), potentially causing intrarenal microthrombus formation, and thus, injury.[49,50]

Acute Tubular Necrosis

Acute tubular necrosis refers to the reversible destruction of tubular epithelial cells with acute suppression of renal function. It is the primary cause of AKI following Hymenoptera envenomation. The pathogenesis of ATN includes i) indirect toxicity of venom i.e. the deposition of pigmented casts such as myoglobin and haemoglobin, due to rhabdomyolysis and intravascular haemolysis respectively, in the renal tubules,[51,52] ii) direct toxicity of venom to tubular cells[(53)] and iii) hypotension/haemodynamic instability caused by venom toxaemia-induced cardiovascular injury and anaphylactic shock.[52,54] ATN predominated in the cortex and outer medulla and was more intense in the proximal tubules. This tubular segment is the most susceptible to the toxic effects of the venom due to greater reabsorption of substances associated with intense metabolic activity, with energy expenditure and vulnerability of the enzyme system. The toxic substances of the venom itself probably contributed to the lesion, especially melittin and phospholipases, which are cytotoxic. The ultrastructural examination of the kidney revealed intracytoplasmic structures resembling myelin figures, which might be lipid accumulations resulting from the altered metabolism of these substances due to ischaemia or to toxic aggression. Some of these structures contained mitochondria compatible with phagocytosed apoptotic corpuscles undergoing digestion or autophagic vacuoles surrounding altered organelles, suggesting that direct toxicity to these organelles may occur in the model.[55] Sandbank et al.[56] detected similar changes in proximal tubular cells in experimental studies in hornet venom suggesting a direct toxic effect of the venom on mitochondria. The immunohistochemical analysis showed the presence of myoglobin in tubular casts as well as in the more apical portions of proximal cells. Muscle actin was also detected in the tubular cells. There is also a possible role of renal ischaemia in the genesis of ATN. The ischaemic lesion of the myocardial infarction type and catecholamine release due to Hymenoptera envenomation may affect the cardiac output and secondarily cause renal ischaemia. Likewise, the action of the venom components, such as vasoactive substances, might cause renal ischaemia.[55] Proximal tubule cells have a limited glycolytic capacity and are more vulnerable to ischaemia than distal tubule cells and cells of thick ascending limb. Although thick ascending limb has high glycolytic potential, the thick ascending limb is also a site of ischaemic lesion due to the precarious oxygenation of the renal medulla.[57-59] It was also noted that haemoglobin in the intratubular casts was not detected when the venom dose was reduced to half with regard to the experiment which has intratubular haemoglobin cast findings.[55]

Acute Interstitial Nephritis

Acute interstitial nephritis (AIN) defines a pattern of renal injury usually associated with an abrupt deterioration in renal function characterised histopathologically by inflammation and edema of the renal interstitium, sparing the glomeruli and the blood vessel. AIN accounted for 15% of cases hospitalised for AKI patients which is due to the immune-mediated tubulointerstitial injury,[60] either IgE mediated or non-IgE mediated.[61] The most common etiology of AIN is drug hypersensitivity; other causes include infection, immune-mediated disease, glomerular disease and idiopathic. Zhang et

al.[62] showed that AKI in the setting of wasp stings is not confined to rhabdomyolysis and ATN only, but also acute allergic interstitial nephritis could be the mechanism. The pathology in AIN is the inflammatory cell infiltrate within the interstitum of the kidney. The inflammatory infiltrate is a mixture of T lymphocytes, monocytes and occasionally plasma cells and eosinophils. Although the exact mechanism of AIN is unclear, it is highly probable that AIN is due to immuno-allergic disequilibrium, mainly cell-mediated immunity supported by the presence of T helper and T suppressor lymphocytes among the cellular infiltrates.[63] However, in some cases, humoural mechanisms are involved with complement proteins, immunoglobulins and anti-tubular basement membrane antibodies found in the interstitium.[60,64]

Acute Cortical Necrosis

Besides the common ATN and less common AIN, acute cortical necrosis (ACN) is the more infrequent cause of AKI. Glomerulus is the most affected part of nephron in ACN, however, the cortical tubules are also adversely affected, leading to both glomerular and cortical tubular necrosis. Kumar et al.[65] reported the first case of ACN leading to AKI following a single wasp sting. The renal biopsy revealed the features of thrombotic microangiopathy. However, he failed to investigate the venom specific IgE level or tryptase level in the serum of the patient to correlate the coagulopathy with venom anaphylaxis. The thrombotic microangiopathy with patchy cortical necrosis has been reported by George et al.[66] in a patient with more than 50 wasp stings, with the clinical course of increased serum total IgE level (venom-specific not assayed), DIC, rhabdomyolysis, hepatic necrosis and acute respiratory distress syndrome. DIC is a striking clinical presentation in snake envenomation, particularly of Viperidae family. Presence of fibrin thrombi in glomerular capillaries and renal microvasculature leads to microangiopathic haemolytic anaemia, thrombocytopenia and cortical necrosis.[66] A single bee sting also unusually caused intravascular coagulation and elevated serum level of allergen-specific IgE. The role of mesothelial injury, thrombocyte and macrophage activation, release of cytokines, leukotrienes, bradykinin and platelet aggregation factor, immune complex deposition in small vessels, and complement activation, is postulated mechanism for intravascular coagulation.[37] The pathogenesis of ACN postulated include i) endothelin induced vasospasm of small vessels, ii) toxic capillary endothelial damage, iii) endotoxin-induced generalised Schwartzmann phenomenon and iv) hypercoagulable state.[67]

Nephrotic Syndrome

The immune disturbances are considered important in the pathogenesis of nephrotic syndrome (NS). It has been postulated that involvement of T lymphocytes and their cytokine secretion influences the permeability of the glomerular basement membrane with consequent development of proteinuria. Hymenoptera stings are a potential factor for the occurrence of NS.[68,69] Tauk et al.[70,71] in his review has reported NS following wasp stings with diverse renal pathological changes, which includes minimal change disease, mesangial proliferative glomerulonephritis, severe glomerular hyalinisation and a mixed pattern of mesangioproliferative glomerulonephritis and early membranous nephropathy.

Renal Tubular Acidosis

Both pRTA[72] and dRTA[34] have been documented after Hymenoptera stings. Ram et al.[53,73] had reported a case of pRTA in a patient after honeybee stings wherein the renal biopsy showed dense lymphocytic interstitial infiltrate and biochemical parameters consistent with pRTA, such as presence of hyperchloremic metabolic acidosis with normal anion gap and hypokalemia with preserved ability to acidify urine to a pH of 5.5 in a steady state along with hypophosphataemia, hypouricaemia, renal glucosuria and high urinary excretion of calcium, phosphorus and uric acid. Animal studies have shown that bee venom or melittin inhibits apical transporters of proximal tubules with evidence of increased fractional excretion of phosphorus, sodium and potassium in urine.[53,73] Han et al.[74] have further shown the involvement of oxidative stress due to bee venom and its melittin-related reactive oxygen species (ROS) generation by proximal tubular cells (PTC) in inhibition of apical transporter of PTC via PLA_2 activation. Melittin from bee venom has been suggested to activate the tissue PLA_2 that induces an increase in arachidonic acid, which attributes to free radical-induced lipid peroxidation.[74] Mastoparan has also been shown to facilitate the PLA_2 activity of both venom and victims.[24] Free radicals play an important role in the pathogenesis of tubular dysfunction, which may lead to necrosis and thus renal failure by their severe cytotoxic effects such as lipid peroxidation and protein denaturation in cell membranes, followed by the changes in membrane fluidity, enzyme properties and ion transport.[74] Likewise, Sanjay et al.[34] reported the case of

dRTA following a wasp sting. These reports try to correlate between Hymenoptera stings and renal tubular dysfunctions, however, further studies are required to elucidate the exact pathogenesis of tubular dysfunction.[34,72]

TREATMENT AND MANAGEMENT

Allergic and toxic reactions are the complications encountered during Hymenoptera stings. The complications range from normal skin reactions to anaphylaxis and multiple organ failure. There are many different species in Apidae and Vespidae family; however, their stings all lead to similar medical conditions, mostly negligible in a medical sense. Symptoms vary by victim, with individual sensitivity and the amount of venom inoculated in the body, both playing important roles. There is no specific treatment for Hymenoptera stings in general and no manufactured antivenom available for severe reaction cases.[75] Treatment consists of cold compresses and analgesics for local reactions. Acute medical therapy for systemic reactions includes standard treatment for anaphylaxis including epinephrine, H_1-receptor antagonists, corticosteroids and other supportive therapy under symptomatic treatment strategy.[76] Venom immunotherapy has also been recommended for patients who exhibit systemic reactions following and inadvertent Hymenoptera sting.[28]

Renal complications do not occur as quickly as anaphylaxis, therefore the follow-up of urine output and colour, urine analysis, blood pressure, haematocrit and renal function tests are essential post-sting standard monitoring parameters.[75] The major treatment strategy is to i) correct the hypovolemia and attend the renal ischaemia, ii) enhance the clearance of haemproteins, toxins or toxic wastes from the circulation and the kidney and iii) alleviate the direct adverse consequences of venom toxins, toxic wastes, electrolyte imbalance and haemproteins on kidneys and other organs.[48] The early pharmacological intervention incorporates the volume replacement and alkaline diuresis in order to prevent the factors that lead to AKI, such as dehydration and renal hypoperfusion, intratubular cast formation and tubular obstruction, aciduria, and free radical release.[77] Haem iron cast formation in the renal tubules is facilitated in patients with acidic urine (pH<5.6) and a high concentration of haemoglobin or myoglobin in the renal tubules, which reacts with Tamm-Horsfall protein (THP) and precipitates, forming casts. Such binding is enhanced under acidic conditions, and thus urinary alkalinisation with sodium bicarbonate is believed to be helpful in reducing cast formation.[78] The ideal regimen for alkaline diuresis in patients with haemolysis and/or rhabdomyolysis is half isotonic saline (0.45%, or 75 mmol/L sodium) to which 75 mmol/L of sodium bicarbonate is added. Furosemide is the popular choice as a diuretic agent. However, once the overt kidney injury has been established, the only reliable therapeutic intervention is extracorporeal blood purification such as intermittent haemodialysis, continuous renal replacement therapy, peritoneal dialysis and plasmapheresis (whenever indicated).[77] The treatment of established AKI is, thus, largely supportive in nature, renal replacement therapy being the cornerstone.[79] Forced alkaline diuresis can avert the need of renal replacement therapy[52] provided it is instituted early after the incident and before the progression of kidney injury, however, the diuretic therapy in AKI remains controversial despite its common use, and awaits for higher quality evidence on diuretic use in AKI.[80]

CONCLUSION

Hymenoptera stings are common medically-significant insect stings. The sting incidents are high during late summer or early fall when there is an increased outdoor activity of human beings or large numbers of vespids are attracted to the foods of humans eating outdoors. The sting or mass envenomation occurs if the insect is disturbed or their hive is interrupted.[13] The sting(s) result into diverse clinical sequelae either due to allergic reactions or due to toxic reactions. AKI is the unusual medical complication developed after Hymenoptera sting(s) with due basis of both hypersensitivity reactions and/or toxic reactions posed by the venom. Provided the timely medical intervention, along with the supportive therapy, there is an adequate evidence of complete and non-recurring recovery of kidney function.

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