Allergies Related to Mosquitoes, Repellents, and Insecticides

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ABSTRACT — Man's skin response to the mosquito bite exhibits great individual variability. The everyday immediate reaction consists of a red, or erythematous wheal that lasts only one or two hours. Twenty to 24 hours after the mosquito bite, a delayed reaction of erythema, swelling, and itching may also occur. An individual may exhibit an immediate reaction, delayed reaction, both reactions, or neither reaction. Studies suggest that sensitization to mosquito saliva may be responsible for the inflammatory response. This hypothesis is supported by histologic studies which demonstrate striking infiltration of inflammatory cells at the site of mosquito bites.

Severe local reactions can occur in areas of compromised circulation. Severe systemic reactions, on the other hand, are extremely rare. Although allergy or hypersensitivity to mosquito saliva is thought to cause both the ordinary and systemic bite reactions, this has not been investigated by modern immunologic methods.

The use of insect repellents is a safe, effective method for avoiding insect bites. However, these agents can cause allergic contact dermatitis or hives. Aerosol insecticides are also effective, but respiratory allergic symptoms can occur in susceptible or asthmatic individuals.

Introduction

The mosquito is found worldwide and has medical importance primarily for its role as vectors of disease. In the tropics, malaria, yellow fever, dengue, and filariasis all are transmitted via the mosquito. In North America, mosquitoes transmit certain arboviruses that cause encephalitis. The female mosquitoes suck blood, while the males are content with nectar. Both man and animals are fair prey for the female mosquito. The following discussion concerns only the human reaction to mosquito bites and will not include discussion of mosquitoes as vectors of disease, nor bites of other insects.

The Normal Mosquito Bite Reaction

Studies have shown that the female mosquito is attracted to dark clothing, heat and humidity, and carbon dioxide. Human sweat is a known mosquito attractant, and psoriatic skin (which is abnormally dry) is less attractive to the mosquito than normal skin. Following attraction of the female mosquito to human skin, the mosquito alights and prepares for her blood meal. The female mosquito has specialized mouth parts modified for piercing mammalian skin and sucking blood. The hollow, needle-like fascicle is flexible at the distal end and thus can penetrate skin at any angle. The female mosquito probes for blood with single (if she is lucky), or more likely, multiple penetrations. The mosquito then may suck blood directly from a capillary or alternatively from a hemorrhage following the rupture of a small blood vessel. During the blood meal, mosquito saliva is deposited into human skin.

The ordinary redness, swelling, and itching from a mosquito bite apparently is an allergic reaction, both of the immediate immunoglobulin E-mediated (the class of immunoglobulins involved in the classic allergic response) and delayed lymphocyte-mediated types. There is great variability in the individual's reaction to a mosquito bite. Mellanby in 1946 (1) documented both immediate and delayed type skin responses. Twenty-five volunteers who had no previous exposure to the mosquito *Aedes aegypti* were deliberately bitten by female mosquitos. There was no immediate cutaneous response other than a red spot 1 mm in diameter. After 20-24 hours, however, there appeared a delayed reaction consisting of a 3 cm red patch that was accompanied by itching. After one month of repeated exposure to the *Aedes aegypti* mosquito, the volunteers were again challenged with a mosquito bite, and on this occasion the subjects developed an immediate cutaneous reaction consisting of a wheal with surrounding redness. This wheal was accompanied by itching, but all signs and symptoms disappeared within two hours. Twenty to 24 hours following this second challenge, a delayed reaction also appeared. Finally, after a further period of exposure to the *Aedes aegypti* mosquito, the subjects were challenged again with mosquito bites and this time exhibited the immediate reaction but no delayed reaction. This sequence of responses consisting of delayed reaction only, followed by both immediate and delayed reactions, followed by immediate reaction only, has been confirmed by others.

However, the individual variability of cutaneous responses to the mosquito should be emphasized. McKiel and West in 1961 (2) evaluated the skin reactions of 211 subjects to the

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Aedes aegypti mosquito. Although none of the subjects had previous exposure to this species of mosquito, 33% of the subjects exhibited an immediate reaction only, and 59% exhibited both an immediate and delayed reaction. Just 5% of these patients exhibited a delayed reaction only, and 3% showed no cutaneous response. These data suggested to investigators that multiple exposure to mosquito bites over time induced varying types of sensitization to the mosquito bite.

This hypothesis was supported by the demonstration that newborn infants exhibit virtually no cutaneous reaction to the bite of the *Aedes aegypti* mosquito. Furthermore, it was postulated that repeated exposure to mosquito bites may eventually lead to a state of desensitization. Killby and Silverman (3) studied the cutaneous responses of mosquito laboratory workers in an attempt to assess the effect of repeated and prolonged exposure. The mosquito handlers were exposed to different species of mosquitoes and were deliberately challenged with several mosquito species. Of the nine workers with increased exposure to mosquito bites, two exhibited virtually no cutaneous reaction to all species of mosquitoes tested. Three individuals exhibited both immediate and delayed responses to all mosquito species tested, and four individuals appeared sensitized to certain species of mosquito and desensitized to others. Six of seven control subjects who did not report previous exposure to mosquito bites demonstrated delayed responses only. One can conclude that individuals with prolonged exposure to mosquitoes also display variability of immediate and delayed responses; some exhibit no reactivity whatsoever. Although the data were insufficient to rigorously assess the species specificity of the cutaneous reactions, it is clear that individuals may respond differently to different species of mosquitoes.

The sensitizing agent in the mosquito bite has been shown to be mosquito saliva. Early experiments showed that extracts prepared from the head and thorax of the mosquito (which contain the salivary glands) elicited a greater cutaneous response when injected into skin than did extracts prepared from the abdominal portion of the mosquito. Hudson et al. (4) convincingly demonstrated that no cutaneous response occurred following a mosquito bite in the absence of saliva. The salivary ducts of 12 anesthetized mosquitoes (*Aedes stimulans*) were cut with sharpened tungsten wire. All 12 mosquitoes failed to produce immediate or delayed responses following bites on human volunteers. Control mosquitoes showed normal reaction patterns. Newsome and colleagues (5) collected the oral secretion of the *Aedes aegypti* mosquito and by gel filtration chromatography were able to purify a high molecular weight protein designated F-1. Immunoelectrophoresis of the F-1 protein using rabbit antiserum against mosquito oral secretion yielded a single precipitin line suggesting that the F-1 protein was indeed the only sensitizing agent in mosquito saliva. Furthermore, when injected into guinea pig skin, the F-1 protein induced immediate skin reactions in a dose-dependent manner.

Hence the normal mosquito bite reaction may consist of an immediate wheal at the puncture site lasting 1-2 hours and accompanied by itching, or a response 20-24 hours following the mosquito bite consisting of redness, swelling, and itching. This cutaneous reaction is thought to be a hypersensitivity response to the F-1 protein in mosquito saliva.

Severe Local Reactions

A mosquito bite on an area of skin that is compromised by poor circulation can lead to severe complications. Such mosquito bites may lead to hemorrhagic or ulcerated lesions accompanied by skin and lymph node infection. These severe local reactions most commoly occur on the legs. Not uncommonly, the inflammation at the site of a mosquito bite may lead to blister formation. Secondary infection can lead to a variety of serious skin infections. The constitutional symptoms of fever and aches may accompany serious secondary infection.

Skin lesions at the site of a mosquito bite may persist for months to several years. On examination, these chronic or persistent insect bites appear to be small, firm, raised lesions. Papular urticaria is a childhood skin disease characterized by clusters of multiple such lesions occurring in a generalized distribution. These lesions may occasionally form blisters and are accompanied by intense itching. The syndrome has a distinct seasonal distribution with increased incidence in the summer months. Papular urticaria was previously thought to be secondary to obscure infection, stress, and food intolerance. It is now known to be caused by multiple insect bites, usually the common bedbug, but occasionally by mosquito bites.

Histology

The histology of the inflammatory reaction of a mosquito bite is similar to the bites of other arthropods. Goldman and colleagues in 1952 (6) performed skin biopsies at various intervals following a bite by the *Aedes aegypti* mosquito. Thirty minutes after a mosquito bite, there is marked swelling of the superficial dermis layer of skin and some infiltration of the polymorphonuclear leukocyte type of white blood cell. Eosinophils (white cells involved in allergic reactions and other conditions) and lymphocytes (white blood cells of the immune response) are present but sparse. Six-hour biopsies show an increase in the spread of inflammation as well as increased white cell infiltration and increased swelling. At 24 hours, the swelling of the dermal layer of skin decreases, and the cellular infiltrate consists primarily of eosinophils and lymphocytes. The cellular infiltration decreases at 48 hours, and at 5 days no swelling is present and only a few lymphocytes persist. The blister reactions demonstrate swelling of the subepidermal layer of skin with dense lymphocyte infiltration around blood vessels. Microscopic examination of local reactions shows dense inflammatory infiltrates extending to the subcutaneous fat. The cellular infiltrate is comprised of white cells including polymorphonuclear leukocytes, lymphocytes, histiocytes, and occasional plasma cells; however, the eosinophilic component of the infiltrate is most striking.

Biopsies of chronic, persistent insect bites reveal dense cellular inflammation around blood vessels composed of polymorphonuclear leukocytes, lymphocytes, histiocytes, eosinophils, and plasma cells. This is similar to the histopathology of papular urticaria. Interestingly, the infiltrates may form secondary lymphoid follicles with germinal centers similar to the pattern found in lymph nodes. Moreover, the reaction of the epidermis may be so advanced as to simulate squamous cell carcinoma (skin cancer). The lymphoid infiltrate and follicle formation may similarly bear close resemblance to true lymphoid malignancies such as mycosis fungoides, Hodgkin's disease, or lymphosarcoma. The relationship of this lymphoid inflammatory reaction to actual lymphoid malignancy (see below) is unclear at the present time.

Severe Systemic Reactions

Hidano and co-workers (7) have suggested that there may be an association between hypersensitivity to mosquito bite

and malignant histiocytosis, a lymphoma-like malignancy. These investigators sent letters to 240 dermatologists and pediatricians in Japan requesting names of patients with mosquito allergy. Twenty-one cases of severe local and systemic reactions to mosquito bite were brought forth and follow-up data compiled. In three cases, the hypersensitivity to mosquito bite resolved spontaneously, and in nine cases no change in hypersensitivity was noted. Nine of the 21 cases died, which represents an extraordinary 43% mortality. Seven of the nine patients died with malignant histiocytosis. The clinical course for these patients typically consisted of unexplained liver and spleen enlargement followed several years later by the onset of fever, anemia, lymph node enlargement, and constitutional deterioration leading to death. Autopsy findings revealed diffuse infiltration of malignant histiocyte cells into lungs, liver, skin, bone marrow, spleen, and lymph nodes. The severe local reaction to mosquito bite usually consisted of erythematous swelling followed by necrotic (destructive) skin infection and ulceration. Skin biopsies when available showed areas of hemorrhage, swelling, and infiltration around blood vessels consisting of polymorphonuclear leukocytes and eosinophils. Whether there is a cause and effect relationship between the mosquito bite hypersensitivity and malignant histiocytosis, whether a transforming agent such as virus is involved, or whether this association is restricted in Japan, is not yet known.

Although allergy or hypersensitivity is thought to play an etiologic role in the pathogenesis of mosquito bite reactions on the grounds of the indirect evidence cited above, this has not yet been carefully investigated by modern immunologic methods. Suzuki and co-workers in 1976 (8) performed multiple immunologic studies to evaluate the role of specific immunoglobulin E in mosquito bite hypersensitivity. They report a 14-year-old girl who exhibited large local reactions consisting of erythematous swelling and ulceration to mosquito bite. These local reactions were accompanied by fever, lymph node enlargement, and subsequent liver and spleen enlargement. Their studies showed that the total IgE was elevated at 5,300 IU/dl and total IgA (a class of immunoglobulin found principally in secretions) was elevated at 1,250 mg/dl. Skin tests to three mosquito species' extracts (*Aedes vaxans nipponii, Culex tritaeniorhynchus,* and *Anopheles sinensis*) were all reported as positive. Specific IgE antibody against mosquito extract was detected by radioimmunoassay. The results of inhibition studies suggested that cross-reactivity between mosquito species existed. However, by double immunodiffusion in agar, no precipitating antibody was detected, suggesting the absence of an IgG response. (IgG is the immunoglobulin that is the principal type of circulating antibody.) Finally, the investigators were able to transfer mosquito hypersensitivity by injecting the patient serum into two normal recipients and evoking a passive cutaneous anaphylactic response. While far from conclusive, these studies suggest that mosquito hypersensitivity in this child may be mediated by specific IgE.

Anaphylaxis following mosquito bite is an extraordinarily rare event. Reactions such as generalized hives following mosquito bite have been reported, but even this reaction is very uncommon. In contrast, anaphylactic symptoms following honeybee sting is a well recognized problem, and similar reactions have been reported from deerfly, horsefly, and fire-ant bites.

Treatment

Since the normal response to the mosquito bite is mild, specific treatment is rarely indicated. Occasionally, a patient may seek assistance for relief of itching. Calamine lotion, lotions containing 0.25% menthol, 1% phenol, or 2% camphor may afford symptomatic relief. Topical steroids or oral antihistamines may be administered in selected cases. Severe local reactions are also treated symptomatically with antipyretics for fever and antibiotics specifically for secondary infection. Although there are sporadic reports of successful immunotherapy in the treatment of mosquito hypersensitivity, no conclusive study has been performed to date. In general, immunotherapy with mosquito extract cannot be recommended at the present time. The optimal recommendation for patients with mosquito hypersensitivity is to avoid the mosquito bite.

Allergy to Repellents and Insecticides

Following World War II, much effort was expended in developing an effective insect repellent. Commercially available insect repellents most commonly contain dimethyl phthalate or diethyltoluamide. These are effective, relatively nontoxic chemicals but may induce untoward reactions in susceptible individuals. Available information comes almost exclusively from isolated case reports. The problem seems to be rare enough that scientific investigations have not been carried out. A typical contact dermatitis reaction may appear 24-48 hours following exposure. An immediate cutaneous eruption 15-30 minutes following exposure to diethyltoluamide, termed contact urticaria, has also been reported (9, 10). An unusual skin reaction consisting of a blister-like eruption on the forearm following contact with diethyltoluamide may also occur (11). Rarely, anaphylactic symptoms of generalized angioedema (swelling) and hypotension (collapse of blood pressure) may follow the topical administration of diethyltoluamide (12).

Home and garden use of insecticide sprays may also be effective in diminishing the patient's exposure to mosquito bite. It should be noted, however, that respiratory allergic symptoms such as asthmatic reactions or hypersensitivity pneumonitis have been produced by use of the insecticide pyrethrum (13, 14), and the organophosphate anticholinesterase insecticides can aggravate preexisting asthma.

Conclusions

The great majority of individuals exhibit a combination of immediate or delayed reactions to mosquito bites. These are most often minimal and trivial inflammatory responses. If a mosquito bite occurs on an area of poor circulation more severe local reactions may occur. Persistent skin lesions and blister reactions are usually self-limited and are not serious health problems unless secondarily infected.

Systemic or life-threatening hypersensitivity responses to mosquito bite are exceedingly rare, unlike allergy to Hymenoptera venom. Measures to avoid mosquito bites should consist of the combined use of light-colored clothing, insect repellent, and spray insecticide when indicated. Fortunately for Minnesotans, mosquito bites are more a source of annoyance than illness.

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