

Skeeter syndrome

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Large local reactions to mosquito bites are underdiagnosed and are sometimes assumed to have an infectious etiology when in fact they are caused by allergenic polypep-

tides in the mosquito saliva.¹ Young children, immune-deficient persons, and immigrants or visitors to an area with indigenous mosquitoes to which they have not been previously exposed are at increased risk for severe reactions to mosquito bites. Here we report how specific and sensitive ELISAs using mosquito salivary gland extract as the antigen enabled us to recognize and to describe skeeter syndrome for the first time. This syndrome is defined as mosquito bite-induced large local inflammatory reactions accompanied by fever. The reactions were initially misdiagnosed as cellulitis and investigated and treated as such, although by history they developed within hours of a mosquito bite, a time frame in which it would have been highly unlikely for an infection to develop.

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FIG 1. At age 21 months, this child was bitten just below the right eye by a mosquito. The insect was brushed away. Swelling at the site of the bite began within 1 hour and was accompanied by redness and warmth. The eye rapidly swelled shut and remained swollen for a week. Blood culture was negative. Later, during the summer, similar reactions occurred after mosquito bites on the lower leg and the ear. The photograph was taken by the child's mother.

CASE STUDIES

We studied 5 otherwise healthy 2- to 4-year-old children with no history of allergy to insect bites who were consecutively referred to the Children's Hospital Allergy Clinic after being diagnosed by their different primary care physicians with "cellulitis," which developed within hours at the site of a witnessed mosquito bite (Fig 1). We also studied 5 age-matched control children with typical local reactions to mosquito bites.

The diagnosis of cellulitis was made on the basis of redness, swelling, warmth, and induration of the entire periorbital region in 2 children and the entire distal extremity (hand and forearm or foot and lower leg) in 3 children, accompanied by low-grade fever and fussiness. Blood cultures were taken, and in 2 children radiographs were obtained to rule out osteomyelitis underlying the extensive soft tissue swelling. In all the children the antibiotic treatment prescribed by the primary care physician was discontinued after 2 to 3 days when the inflammatory reaction was beginning to subside and the cultures were reported as negative. The swelling, redness, warmth, and induration gradually disappeared over the next 3 to 10 days.

Months after the diagnosis of cellulitis was made, the children were referred to the allergy clinic. The diagnosis of skeeter syndrome, a mosquito bite-induced large local inflammatory reaction accompanied by mild systemic symptoms, was confirmed by using an indirect ELISA¹ to measure specific IgE and specific IgG subclasses to salivary gland antigens of the predominant indigenous mosquito *Aedes vexans*, which cross-react with salivary gland antigens from other mosquito species.^{2,3} These antigens were prepared by dissecting the glands from the heads and thoraxes of approximately 370 female *A vexans* mosquitoes and dispersing them in 1 mL of 0.02 mol/L PBS by sonication.¹ The monoclonal antibodies for measurement of IgG subclasses were obtained from Caltag Lab-

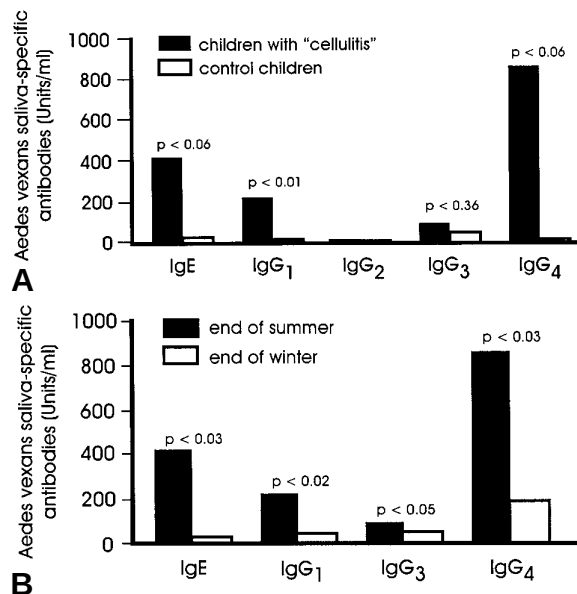


FIG 2. A, Significantly elevated serum concentrations of *A vexans* saliva-specific IgE, IgG1, IgG3, and IgG4 were found in children with skeeter syndrome (mosquito bite-induced large local inflammatory reaction originally diagnosed as cellulitis) in contrast to age-matched control children. IgG2 was not detectable. **B,** Seasonal variation in *A vexans* saliva-specific IgE, IgG1, IgG3, and IgG4 in children with skeeter syndrome. Antibody concentrations declined significantly during the cold winter months when no exposure to mosquitoes occurred.

oratories (San Francisco, Calif). The ELISA results were calculated by interpolation from the dilution curve of a reference serum, which was pooled from the sera of children with skeeter syndrome.

Serum concentrations of IgE, IgG1, IgG3, and IgG4 to *A vexans* salivary gland antigens were significantly elevated in the children with skeeter syndrome compared with control children (Fig 2). The *A vexans*-specific IgE, IgG1, IgG3, and IgG4 concentrations decreased significantly during the ensuing cold winter months when no exposure to mosquitoes occurred. In Western blotting,² sera from children with skeeter syndrome reacted with 8 to 15 *A vexans* salivary gland antigens, and sera from control children did not.

DISCUSSION

The large local reactions to mosquito bites that we have designated as skeeter syndrome occur within hours of the bites and are characterized by the cardinal signs of inflammation: swelling (tumor), heat (calor), redness (rubor), and itching/pain (dolor). By inspection and palpation, it is impossible to differentiate between inflammation caused by infection and inflammation caused by an allergic response. Because most mosquito bites are unwitnessed and painless, the exact time interval between the bites and the reactions is usually unknown, and the cause-and-effect relationship is seldom apparent. Skin tests with commercially available nonstandardized mosquito whole body extracts, which may contain little mosquito saliva antigen, cannot be relied upon for diagnosis.⁴ Mosquito bite challenges are not recommended because of the risk of disease transmission through the bite and the risk of causing an allergic reaction in a sus-

ceptible patient. Here we report the usefulness of specific and sensitive ELISAs in the clinical diagnosis of mosquito allergy.

Several salivary antigens of *A vexans* have been identified as being shared with other mosquitoes that have a worldwide distribution, including *A aegypti*, the most important human mosquito pest.^{2,3} Because of the extensive cross-reactivity of antigens among mosquito species, the skeeter syndrome identified in midwestern Canada has global clinical relevance. The process of obtaining mosquito salivary glands or mosquito saliva is extremely time consuming and labor intensive. The specific diagnosis of mosquito allergy therefore will eventually be facilitated by the development of recombinant mosquito salivary antigens. Three such allergens, a 68-kd antigen that functions as an anticoagulant and is known in recombinant form as rAed a 1, and 37- and 30-kd antigens with unknown functions named rAed a 2 and rAed a 3, respectively, have already been synthesized.^{5,6} Both rAed 1 and rAed 2 antigens cloned from *A aegypti* are shared with *A vexans* and with other mosquito species.²

In addition to IgE, IgG (especially IgG4 and IgG1) appears to play an important pathogenic role in mosquito allergy. An early rise in both serum IgE and IgG levels has been found during prospective monitoring of natural sensitization and desensitization to mosquito bites in an adult⁷; also, in a cross-sectional study, serum mosquito salivary gland-specific IgG levels correlated significantly with the size of the immediate skin reaction to mosquito bites and with salivary gland-specific IgE levels.¹

The children with skeeter syndrome remain healthy, except for recurrent large local inflammatory reactions to mosquito bites. Although we have the clinical impression that their long-term prognosis will be favorable, this

needs to be documented in a prospective study. Natural desensitization may take years to occur because it depends on the frequency and intensity of their exposure to mosquitoes, which must be minimized on account of their severe reactions. Recognition of skeeter syndrome may facilitate avoidance of unnecessary diagnostic procedures and unnecessary antibiotic treatment in affected children.

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