A study on the role of lepidopterism in seasonal fever outbreaks

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ABSTRACT

Fever is one of the most common reasons for visit in primary care practice. Outbreaks of fever that occur at certain areas in a seasonal manner are usually recognized early by diligent general practitioners in primary care settings. At the community level, in order to tackle seasonal fever outbreaks, prevention and control strategies are widely implemented, targeting the locally prevalent endemic infectious diseases. However, what about seasonal outbreaks of diseases because of non-infectious endemic causes? How well are we aware of this and how prepared are we? In 2006, there was an outbreak of Chikungunya fever in Kerala, a southern state in India. A group of scientists discovered that many patients assumed to have Chikungunya also had exposure to a specific type of lepidopteran moth, Asota caricae, also known as tiger moth. Further research revealed that rats exposed to live tiger moths under experimental conditions produced features resembling Chikungunya and similar viral fevers, with symptoms comprising fever, arthralgia, arthritis, and thrombocytopenia. A moth-toxin-specific immunoglobulin E (IgE) antibody was identified in sera of patients who recalled exposure to tiger moths.

Aims: 1. To screen subjects with clinical features resembling viral fevers for specific IgE antibodies against tiger moth toxin. 2. To assess the role of tiger moths in producing features resembling viral fevers in humans.

Settings and Design: This hospital-based, cross-sectional analytical study was conducted from March 2015 to March 2016 in a tertiary hospital in North Kerala. The sample population included patients who had clinical manifestations suggestive of viral fevers and presented to the outpatient departments of Family Medicine, Internal Medicine, or Emergency Medicine and satisfied the inclusion criteria.

Methods and Material: After collecting the informed consent, the blood sample needed for the study was collected simultaneously with the blood collected for other tests ordered by the consulting doctor. No extra needle insertion was needed for the study. A total of 234 samples were examined for the presence of moth-toxin-specific IgE antibodies.

Statistical Analysis Used: Data were analysed using SPSS 17.0. Graphs were produced using Microsoft Excel. Categorical variables were expressed as frequencies with percentages and analysed using Chi-square test/Fisher’s exact test. Incidence/prevalence was also expressed in percentages with confidence interval. The continuous variable was expressed as mean with standard deviation or median with inter-quartile range. For all tests, a probability value (p value) < 0.05 was considered statistically significant.

Results: Among the 234 subjects who were screened in the 13-month period, 44 subjects (18.8%) tested positive for moth-toxin IgE, of which 28 were males and 16 were females. The maximum percentage of samples with positive moth-toxin IgE antibodies was detected during the months of March, June, July, November, December, and January. Out of the 44 subjects who had positive moth-toxin IgE antibodies, 24 tested positive for Dengue fever (of which eight were positive for the Dengue NS1 antigen, 11 were positive for the Dengue IgM antibody, and five were positive for both Dengue NS1 antigen and Dengue IgM antibody), two tested positive for Leptospirosis IgM antibody, two tested positive for Rickettsial antibody, and three had a positive Widal test. It was found that association of moth-toxin IgE with all the presenting symptoms of subjects analysed in this study was not statistically significant, except for lymphadenopathy. Skin rashes of different morphologies were seen in the study group. 20.5% (n = 9) of the subjects who tested positive for moth-toxin IgE had skin rashes. A majority of these were erythematous and maculopapular rashes, with incidence of 44% (n = 4) and 33% (n = 3), respectively.

Conclusions: 1. A seasonal variation is evident in the incidence of cases with positive moth-toxin IgE. 2. There is no significant age/sex preference for moth-toxin IgE positivity. 3. Subjects who tested positive for moth-toxin IgE also had positive serological tests for other infectious causes of fever, including Dengue fever, Leptospirosis, Enteric fever, and Rickettsial fever. The role of tiger moth exposure in

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producing fever and related symptoms hence needs to be studied further. 4. It was observed that moth-toxin IgE had significant association with lymphadenopathy. This should be investigated in further studies. 5. Even though the role of lepidopterism in seasonal fever epidemics is not clear, primary care physicians should be more aware of such entities which can present with a wide range of manifestations.

Keywords: Asota, Chikungunya, Dengue, fever, Kerala, lepidopterism, tiger moth

Introduction

Fever is one of the most common reasons for visit in primary care practice.[1] More than 25 lakh cases of undiagnosed seasonal fevers are reported every year in Kerala.[2] Most of these cases, reported from various regions, with a wide range of symptoms, are generally assumed to be of viral aetiology, based on clinical features, and without being tested for any specific viral markers.

At the community level, in order to tackle seasonal fever outbreaks, prevention and control strategies are widely implemented, targeting the locally prevalent endemic infectious diseases. However, how well have we considered the non-infectious endemic diseases? Can they mimic such seasonal fevers? How well are the primary care physicians, as the first point of contact in a community setting, aware of this entity and its effects?

Moths are known to have a seasonal variation in population depending on temperature, humidity, and rainfall.[3,4] Interestingly, maturation of a particular type of lepidopteran moth, *Asota caricae Fabricius* (Lepidoptera: Noctuidae: Aganainae), also known as tiger moth, which is distributed widely across South Asia, occurs in a seasonal manner that coincides with fever epidemics. Moths and butterflies, although ubiquitous across almost every geographical terrain with immense opportunities for exposure to humans, are rarely considered as vectors for transmission of pathogens. It is intriguing whether exposure to these insects can cause any manifestations in humans.

Lepidopterism refers to the symptoms in humans caused by exposure to parts or products of moths and butterflies during various stages of their life cycles. This may or may not have cutaneous symptoms. Contact with caterpillars, moths, cocoons, or parts thereof can cause purely cutaneous reactions, known as Érucism.[5-7]

Cutaneous reactions of lepidopterism are of three different types: wheal and flare reactions, toxic irritant dermatitis, and persistent itchy papules. Other reported signs are conjunctivitis, pharyngitis, malaise, and upper respiratory tract symptoms including respiratory distress.[8-12] Systemic manifestations reported include nausea, fever, dizziness, tiredness, and arthralgia.[13,14]

Various chemicals have been isolated from caterpillars, setae, moths, and eggs of different species of Lepidoptera, which include histamine, acetylcholine, and formic acid.[15] Exposure of live tiger moths to experimental rats is known to cause pyrexia, arthritis, thrombocytopenia, altered liver enzymes, and renal parameters.[16] It can also result in extensive lymphocytic proliferation in peri-bronchial regions with evidence of recruitment of mast cells in bronchioles, as seen by necropsy, with both known to release pulmonary histamines.[16,17]

In an earlier reported study conducted in a tertiary centre in Kerala, persons exposed to the moth toxin were found to have immunoglobulin E (IgE) antibodies specific against it. By using the Western Blot technique, moth-toxin-specific antibodies had been identified in 48 out of 155 patients. Their symptoms had resembled viral fevers, but they were found to be negative to commonly performed specific viral markers such as dengue.[4]

Screening for moth-toxin-specific IgE antibodies in patients presenting as viral fevers would reveal the prevalence of exposure to such tiger moths, which are known to cause allergic manifestations in humans. Studying the symptomatology in patients with moth-toxin-specific IgE antibodies may prove beneficial in identifying the role in mimicking viral fevers and clinching any differentiating features. Further, the role of prevention and anti-allergic medications in such instances may be studied.

In a primary care setting, keeping a tab on such seasonal outbreaks of allergic manifestations can aid physicians not only to promptly diagnose and manage efficiently but also to promote preventive strategies. Information campaigns and health education may promote the development of preventive attitudes that can reduce the contact between the urticant moth setae and human populations: reduction of light sources, regular cleaning of furniture exposed to the moth setae, wearing of protecting clothes, etc.[18,19]

Aim of the study

1. To screen subjects with clinical features resembling viral fevers for specific IgE antibodies against tiger moth toxin.
2. To assess the role of tiger moths in producing features resembling viral fevers in humans.

Objectives of the study

1. To study the prevalence of moth-toxin-specific IgE antibodies in the study population.
2. To compare the symptomatology between febrile patients with a positive titre of moth-toxin-specific antibodies and those with a negative titre of moth-toxin-specific antibodies.
Subjects and Methods

This hospital-based, cross-sectional analytical study was conducted from March 2015 to March 2016 in a tertiary hospital in North Kerala.

The sample population included patients who had clinical manifestations suggestive of viral fevers and presented to the outpatient departments of Family Medicine, Internal Medicine, or Emergency Medicine and satisfied the inclusion criteria.

Inclusion criteria
Fever with any one or more of the following:
• Chills
• Vomiting
• Headache
• Body ache
• Breathing difficulty
• Itching
• Diarrhoea.

Exclusion criteria
1. Patients who were not willing to take part in the study.
2. Children less than 10 years of age.
3. Patients with multi-organ dysfunction.
4. Patients with platelet counts less than 50,000/cu.mm.

After collecting Informed Consent, the blood sample needed for the study was collected simultaneously with the blood collected for other tests ordered by the consulting doctor. No extra needle insertion was needed for the study. A total of 234 samples were examined for the presence of moth-toxin-specific IgE antibodies.

The Western Blot procedure was employed for detection of IgE antibodies. Four millilitres of a patient’s blood was collected. Tiger moth total protein samples were extracted with the protein lysis buffer. The purified protein was quantified using Bradford reagent, and 50 micrograms of the protein was loaded on each well of polyacrylamide gel. After the gel run, the separated proteins were transferred to a polyvinylidene fluoride membrane and blocked with 3.0% bovine serum albumin for 1 hr. The membrane was then cut into strips using Ponceau stain. The strips were blotted individually with the patient’s sera overnight at 4°C. After washing with Toubins buffer, the strips were then blotted with the anti-human IgE horse radish peroxidase (HRP) secondary antibody for 2 hours at room temperature. After the wash steps, the strips were subjected to color reaction with diaminobenzidine (DAB). HRP reacting with DAB yielded brown-colored bands, which indicated positive cases.

Statistical methods
Data were analysed using SPSS 17.0. Graphs were produced using Microsoft Excel. Categorical variables were expressed as frequencies with percentages and analysed using Chi-square test/Fisher’s exact test. Incidence/prevalence was also expressed in percentages with confidence interval. The continuous variable was expressed as mean with standard deviation or median with inter-quartile range. For all tests, a probability value (p value) < 0.05 was considered as statistically significant.

Ethical considerations
This study was conducted following approval from the Institutional Scientific and Ethics committees.

Results
Among the 234 subjects who were screened in the 13-month period, 44 subjects (18.8%) tested positive for moth-toxin IgE, of which 28 were males and 16 were females.

The mean age of the study group was 41 years. The minimum age and maximum age of the study group were 10 and 88, respectively. Out of 44 subjects who tested positive for moth-toxin IgE, most subjects were from the age group of 30–59 years (54.5%), which was not statistically significant.

The maximum percentage of samples with positive moth-toxin IgE antibodies was detected during the months of March, June, July, November, December, and January [Figures 1 and 2].

Out of the 44 subjects who had positive moth-toxin IgE antibodies, 24 tested positive for Dengue fever (of which eight were positive for the Dengue NS1 antigen, 11 were positive for the Dengue IgM antibody, and five were positive for both the Dengue NS1 antigen and Dengue IgM antibody), two tested positive for the Leptospira IgM antibody, two tested positive for the Rickettsial antibody, and three had a positive Widal test [Figure 3].

It was found that association of moth-toxin IgE with all the presenting symptoms of subjects analysed in this study was not statistically significant, except for lymphadenopathy [Figure 4].

Skin rashes of different morphologies were seen in the study group. 20.5% (n = 9) of the subjects who tested positive for moth-toxin IgE had skin rashes. A majority of these were erythematous and maculopapular rashes, with incidence of 44% (n = 4) and 33% (n = 3), respectively.

The mean value of minimum thrombocyte count (in lakhs/microlitre) observed for subjects who tested positive for moth-toxin IgE was 0.94, and for those who tested negative for moth-toxin IgE, the mean value was 1.07, which was not statistically significant.

Discussion
In the current scenario of widespread fever outbreaks, it is essential to explore the evolving diversity among common pathogens and investigate for new sources. Lepidopterism is one such under-studied area.
It was observed that the maximum percentage of moth-toxin IgE positive cases was detected during the months of March, June, July, November, December, and January. This is comparable with the seasonal variation of tiger moth infestation reported by Wills et al.\[4] in 2016, according to which erratic outbreaks occur from January to April but aggregate as a mild wave in May, followed by huge waves in June to August, which then decline in September through December. However, since the moth-toxin IgE level estimation is being done at a tertiary centre, the potential for variations, especially waning of IgE levels, because of delay in presentation and prior treatment received should be taken into consideration.

A statistical significance was found in the relation between moth-toxin IgE levels and lymphadenopathy. Lymphadenopathy may be correlated with the necropsy findings seen in the lung of rats exposed to live tiger moths, showing lymphocyte proliferation around bronchioles.\[4] Nevertheless, taking into consideration the small sample size, further studies on lepidopterism should re-assess this association. No other symptoms or signs were found to have a statistically significant association with moth-toxin IgE-positive patients.

The findings of this study partly correlate with those of another study reported from Kerala where moth-toxin IgE was positive in patients during fever outbreaks with other manifestations including maculopapular or petechial rash, soft tissue necrosis with extensive sloughing and hyper-pigmentation, fever with chills, headache, nausea, vomiting, diarrhoea, sore throat, ecchymosis, large hives, oedema, crippling arthralgia, arthritis, conjunctivitis, pharyngitis, respiratory distress, thrombocytopenia, electrolyte imbalance, and multi-organ dysfunction.\[4,20–22] It may be said that these patients have similar presenting symptoms to the seasonal viral fevers; however, this relation needs to be assessed in further studies with a larger population.

We found that moth-toxin IgE was tested positive in patients who also tested positive for Dengue NS1, Dengue IgM, Leptospira IgM, Rickettsial Ab, and Widal test in separate instances. This raises the question of what role tiger moth exposure has played in disease manifestation in these patients. Apart from

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**Figure 1:** Seasonal pattern of Moth-toxin IgE results

**Figure 2:** Seasonal pattern of percentage of Moth-toxin IgE positivity

**Figure 3:** Serological positives in patients with positive Moth-toxin IgE
the possibility of the symptoms being induced by tiger moth exposure, one may also consider the chances of triggering of disease manifestations in subjects with sub-clinical infections corresponding to the above-mentioned serologies upon an immuno-suppressed state resulting from tiger moth exposure, or maybe does the tiger moth exposure have no role to play in causing the symptoms? Nonetheless, any synergistic effect because of exposure to tiger moths in patients with other infectious diseases needs to be studied. This is important in clinical medicine, especially in a primary care setting, as the vast majority of patients with symptoms resembling viral fevers present initially at primary/secondary healthcare facilities. Primary care physicians/family physicians hence should be aware of lepidopterism, its seasonal character, and the wide range of manifestations for efficient acute management and to implement preventive strategies.

Conclusions

1. A seasonal variation is evident in the incidence of cases with positive moth-toxin IgE.
2. There is no significant age/sex preference for moth-toxin IgE positivity.
3. Subjects who tested positive for moth-toxin IgE also had positive serological tests for other infectious causes of fever, including Dengue fever, Leptospirosis, Enteric fever, and Rickettsial fever. The role of tiger moth exposure in producing fever and related symptoms hence needs to be studied further.
4. It was observed that moth-toxin IgE had significant association with lymphadenopathy. This should be investigated in further studies.
5. Even though the role of lepidopterism in seasonal fever outbreaks is not clear, primary care physicians should be more aware of such entities which can present with a wide range of manifestations.

Recommendations

1. Since there is overlapping of symptoms between moth-toxin-positive cases and the rest of the seasonal fevers, further studies on effects of moth toxin in humans should be conducted. Symptom analysis and severity of the illness should be studied in detail in patients tested positive for any seasonal fevers and having positive moth-toxin IgE. Studies involving detection of moth-toxin IgE and other serological tests for common seasonal infectious diseases in asymptomatic subjects should be conducted to understand its role in fever and possibility of sub-clinical disease.
2. Correlation between moth-toxin IgE and lymphadenopathy may be addressed in further studies.
3. Precautions and protective measures may be advocated to prevent moth infestations and the harmful effects.

Limitations

1. A wider serological panel testing to rule out all other common causes of fever pertinent to the study population could have shed more light into the scenario.
2. IgE estimation might be altered because of delay in presentation to the study centre and prior treatment received from other centres.

Key take-home messages

Lepidopterism refers to a spectrum of symptoms in humans, ranging from cutaneous to systemic, caused by exposure to parts or products of moths and butterflies during various stages of their life cycles.

In a primary care setting, keeping a tab on seasonal outbreaks of allergic manifestations can aid physicians to promptly diagnose and manage efficiently as well as to promote preventive strategies.

Even though the role of lepidopterism in seasonal fever outbreaks is not clear, primary care physicians should be more aware of such entities which can present with a wide range of manifestations.

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Conflicts of interest
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