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Recent insights on cockroach allergy disorders, diagnosis and management strategies

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Abstract

Globally there has been a rise in allergy conditions, posing significant health as well as a financial burden. The effectiveness of environmental treatments aimed at minimising exposure to cockroach allergen has given contradictory outcomes. Hence, this review aims to expedite an informative account of allergy disorders associated with cockroaches, diagnosis, the immunotherapy role in the management of allergic disorders and drawbacks. Suggestions also have been proposed on how to overcome them. Approaches based on recombinant cockroach allergens were effective in in-vitro & in-vivo appraisal of sensitization for the diagnosis of cockroach allergens. To manage allergic asthma, a comprehensive, step-by-step method has been suggested. This review proposes that using purified recombinant or natural allergens or derivatives of hypoallergenic allergen have the ability to increase cockroach immunotherapy's efficiency consistently and surmount the constraints of utilizing crude cockroach natural extracts. This review article delineates and proposes that immunotherapy utilizing low strength, non-standardized cockroach crude extracts have endeavoured with impressive outcomes. However, there are inadequate outcome reports. Subcutaneous and Sublingual cockroach immunotherapy was deemed safe in children and adults. The recombinant allergens' use for the purpose of diagnosis could aid in the selection of the most suitable cockroach allergens for diagnosis as well as treatment.

Keywords: Cockroach; Allergens; Immunotherapy; Recombinant allergens.

Introduction

Cockroaches are known to be transmitters of several infectious illnesses and are present commonly in urban residences worldwide [1]. The commonest species of domiciliary cockroach are Blattella germanica (Bla g; German cockroach: GC) and Periplaneta americana (Per a; American cockroach: AC) (Figure 1). 2 of these species, AC and GC, seem to be the focus of cockroach allergy study. German cockroach (GC) is a little cockroach that measures around 3-quarters of an inch in length and is usually infested at homes. AC is a big cockroach that measures around Two inches long that infests hospitals, homes, schools, and other huge buildings. The American cockroach is less productive compared to the German cockroach and requires humidity and high temperatures (about 27°C) for optimum growth of population. German cockroach usually prefers dry and cool climates like the USA and Europe, while the larger American cockroach (35 to 53 mm vs. 16 mm in length) favours humid and hot climates like those found in tropical countries such as Brazil, Thailand and Taiwan [2]. Out of 4,500 identified cockroach species, the GC, brown-banded (Supella longipalpis), AC, dusky or smokey brown (Periplaneta fuliginosa) and Oriental (Blatta orientalis) are the only 5 species that are commonly seen in houses as well as possibly contribute to indoor allergens. Indoor allergens are produced by aerosolized proteins originating from cast skins, se-

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cretions, faeces, saliva, dead bodies and debris of cockroaches and can trigger IgE-mediated hypersensitivity reactions as well as allergy-related diseases [3]. Eczema, asthma and allergic rhinitis have become the commonest chronic disorders afflicting children all around the world [4,5]. Several studies have found that the prevalence, as well as the economic burden of these illnesses, have increased in recent decades [6,7]. The cockroach is a well known inhalant allergens' source in asthma and allergic rhinitis. In 1964, Bernton and Brown [8] were among the first to reveal that out of 755 allergy clinic subjects, 44 percent of them had positive skin tests to cockroach antigens [9]. Following the inhalation of cockroach allergens by sensitised asthma subjects, Kang et al. discovered a causal connection between asthma and cockroach allergy [9]. As a result, numerous studies revealed that asthmatic patients in several urban or inner cities worldwide, as well as Seoul, are typically sensitized to this insect [10].

Figure 1: Difference between American and German cockroach [Picture source: Cooper Pest Solutions]

Allergy reactions are on the rise worldwide, posing significant health as well as an economic burden. Therapy for these illnesses is not streamlined, unlike other ailments, due to their highly personalised nature. Indoor allergens are usually overlooked as minor health concerns, but their aggravating effect makes them a matter of severe concern. While unprecedented strides in immunology have disclosed the etiology and treatment to a large extent, missing links exist, comprehension of which for novel therapeutic avenues need research & development on a massive scale. Various researches have benefited from the direction of functional elucidation, allergen identification, recombinant allergen development, immunotherapy, IgE specificity, epitope mapping, etc. In 2001 Allergic Rhinitis and Impact of Asthma (ARIA) documented by WHO established that immunotherapy comprising Sublingual Immunotherapy (SLIT) route administration be started in early life, but minimal age of starting treatment was not specified [11]. Though they are limited and multipronged approaches are required for treating them. With this scenario, this review aims to expedite an informative account of allergy disorders associated with cockroaches, diagnosis, and the immunotherapy role in the allergy disorders' management associated with cockroaches. This review emphasizes the present approaches, drawbacks and proposes solutions to overcome them.

Cockroach allergy and respiratory allergic diseases

Respiratory allergy disorders like rhinitis and asthma are the commonest ailments linked to cockroach infestation of residences in the US and other regions of the world. For nearly fifty years, cockroach allergy has been identified as a significant asthma cause. In 1964, Bernton & Brown reported positive skin prick test (SPT) reactions to the allergen of cockroaches (44 per cent) for the first time, in a landmark study of seven hundred fifty-five allergy clinic subjects in New York. They also discovered that thirteen percent of subjects who were initially assumed to be nonatopic were sensitive to the allergen of cockroaches alone [8] proved the causal association among both asthma and cockroach allergy, demonstrating early, late-phase, and dual bronchoconstriction in sensitised asthmatic subjects after inhaling cockroach extract [9]. In the United States, exposure and sensitization to the allergens of the cockroach are related to high asthma morbidity, particularly amongst lower socio-economic communities like Hispanic, African Americans and Asian populations. Researchers showed that having sIgE (specific IgE) to cockroaches was linked to a higher risk of asthma hospitalizations and use of corticosteroids in asthmatic children population in inner-city regions of the United States [2,12]. Specific features of cockroach allergens, comprising proteolytic activity, were postulated in contributing to more severe disorders linked to cockroach sensitization. Consequently, cockroach allergy is a vital factor of risk for asthma-associated hospitalizations and emergency unit visits. The NCICAS (National Cooperative Inner-City Asthma Study) has recently verified that the association of exposure and sensitization to the allergens of cockroaches is the main factor of risk for asthma morbidity among children from large cities in the United States of America. The NCICAS investigated the bedroom cockroach allergen levels in dust, asthma morbidity and SPT sensitivity in four hundred seventy-six children with asthma. Children with the combination of a positive SPT reaction to extract of cockroach and a bedroom level of Bla g 1 >8 U/g of dust had considerably more parent-reported wheezing, asthma hospitalizations, and unscheduled medical visits compared to other children [13]. When cockroach-allergic asthmatic subjects are compared to ragweed asthma patients as well as asthmatics in general, distinct properties of cockroach asthma are revealed. The commonest clinical presentation of asthma subjects with cockroach allergy is a history of perpetual asthma that might be worsened in the winter. General asthma subjects have notably low levels of serum IgE antibodies in comparison to cockroach allergic patients. In comparison to generalasthmatics, cockroach asthmatics are more prone (32% of patients) to be dependent on steroids. Hence, cockroach asthma is a severe form of allergy asthma that requires more attentive and serious research [3,14-16].

Cockroach allergy immunity mechanisms

In addition to genetic aspects, different adaptive and innate immune mechanisms help in cockroach allergy development. (Figure 2) [17]. The impact of cockroach extracts on human airway epithelial cells, including cytokines and chemokines induction (IL-8, IL-25, IL-33, CCL20, and GM-CSF), are being recorded [18-20]. Proteases acting on protease-activated receptors (PAR-2) mediates some of the effects [21,22]. In mouse models, additional mechanisms of action were discovered. First, GC frass was seen to affect the production of neutrophil cytokine directly through TLR2, but not TLR4, implying a crucial connection between adaptive and innate immunity [23]. Second, by activating the signalling linked to the aryl hydrocarbon receptor (which responds to environmental stimuli and is involved in the asthma pathophysiology), the lungs could be protected from cockroach-induced inflammation [24]. Third, using α-1,3 glucan, the neonatal mice were immunized, which generated IgA-secreting B cells hence inhibiting the cockroach allergy from developing [25]. The majority of these research used extracts of cockroaches, which are known to be notably varied in content

[26]. The discovery of twelve classes of cockroach allergens during the last two decades has allowed researchers to investigate allergen-specific action mechanisms. Amongst these, there is proof of the carbohydrates role on the Bla g 2 interaction with the mannose receptor C-type lectin (CD206) in human circulating fibrocytes. These carbohydrates, which are mostly small mannose terminated glycans without and with fucose, promote the (TNF-, IL-6) inflammatory cytokines' up-regulation and signalling molecules' activation like the NF-kB (nuclear factor-kappa B) [28]. Down-regulating release of IL-12 & toll-like receptor 9, promoting TIM4 (T cell immunoglobulin mucin domain 4) expression in dendritic cells, up-regulating the expression of protease-activated receptors on murine mast cells and inducing the release of T-helper type 2 cytokine are all impacts of group 7 allergens which contribute to Th2 polarisation [29,30].

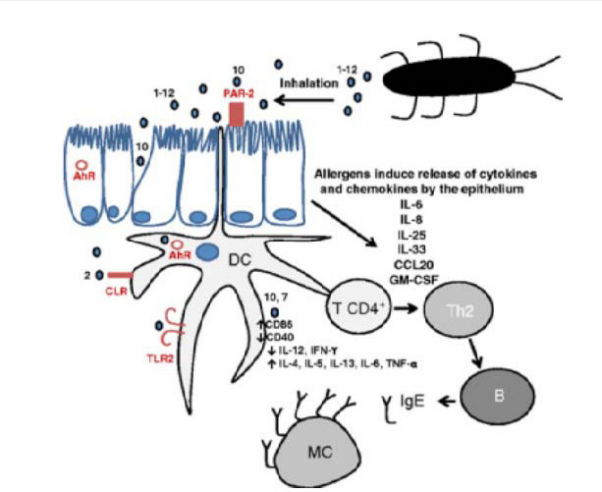

Figure 2: Cockroach Allergy mechanisms. Allergens of cockroach, which belongs to twelve distinct groups, are carried by particles that are inhaled by the human lung, where they activate adaptive and innate immune responses. In the process, the mechanisms involved comprise.
a) epithelial integrity disruption by proteases (such as Per a 10) that enable penetration of allergen,
b) activating pro-inflammatory cytokines release from the epithelium in a PAR-2 dependent manner by proteases,
c) interaction of allergen with different receptors (some of which helps in the allergens uptake by dendritic cells - Toll-like receptors, C-type lectin receptors -), and subsequent adaptive immunity activation with the IgE antibodies production that bind to the high-affinity IgE receptors on mast cells. Figures indicate the allergen group number. Toll-like receptors: TLR, C-type lectin receptors: CLR including mannose receptors, Aryl hydrocarbon receptor: AhR, dendritic cell: DC; T CD4+ and Th2: T cells; B: B cell; mast cell: MC
Adapted from: Pomés et al. 2017 [27]

Cockroach allergens- diagnostic approaches

Cockroach allergy diagnosis in clinical practice is done utilising crude extracts by in-vivo skin testing or/and invitro sIgE measurement to the cockroach. In the United States, the available cockroach extracts for diagnosing allergy are highly variable in allergen content, have low effectiveness and are non-standardized in comparison to extracts of standardized cat, mite or grass [32,33]. Efforts to standardize extracts of cockroach have been hindered by the fact that no single allergen of cockroach is immune dominant, in a way that it may perhaps be measured as a marker for the purpose of standardization [34]. For In-vitro and In-vivo evaluation of sensitization, the use of recombinant cockroach allergens has shown to be promising [35]. Patients allergic to cockroach have varied profiles of allergen sensitization, with no major allergen making up for the majority of sIgE reactivity to cockroach in a given populace. The significance of individual allergens in inducing sensitization differs in various regions of the world, probably owing to the impact of sensitization to cross-reactive antigens.

As per research conducted in the United States, sensitization to Bla g 5, Bla g 2 as well as Bla g 4 showed maximum prevalence in asthmatic patients allergic to cockroach, and a 5 recombinant allergens' panel (Bla g 5, Bla g 4, Bla g 2, Bla g 1 and Per a 7) might detect sixty four percent of patients allergic to cockroach in the US [36]. In a research conducted in Taiwan, Chuang et al. used recombinant Bla g 7, Bla g 5, Bla g 4, Bla g 2, Bla g 1 & the recently discovered vitellogenin, arginine kinase and B. germanica enolase to show that all patients allergic to cockroach responded to at least 1 allergen on an IgE dot-blot immunoassay [37]. Bla g 2 (63 percent) had the highest IgE recognition prevalence, tailed by Bla g 4 (53 percent), vitellogenin (forty seven percent), arginine kinase and Bla g 1 (34 percent), Bla g 7 & Bla g 5 (31 percent), and enolase (27 percent) (25.0 percent).

As previously stated, sIgE-binding to Per a 2 was discovered more often in subjects with persistent asthma in comparison to subjects with only rhinitis (81 percent versus 45 percent) in Taiwan. The findings revealed that sensitization to Per a 2 might be an indicator of more severe airway illness [38]. Individual recombinant & natural cockroach allergens' availability will make it easier to diagnose individual IgE reactivity profiles & identify the effect of specific allergen/s on each cockroach allergy subject.

Cockroach allergies- management options

In the year 2007, NHLBI (National Heart, Lung, and Blood Institute) Asthma Treatment Guidelines proposed a multimodal, stepwise methodology to manage allergic asthma [39]. In subjects older than 5 years and below sixty years who need low to medium dose controller medication, the guidelines recommend avoidance of the allergen, allergen immunotherapy consideration and standard asthma pharmacotherapy.

Cockroach environmental control

Using techniques to decrease environmental cockroach exposure has had varying success degrees. A comprehensive Practice Parameter produced by a Joint Task Force of the 3 major U.S. professional allergy organisations recently summarised cockroach abatement approaches [34]. Crucially, measures that efficiently reduce the levels of cockroach allergen seem to be clinically beneficial as well. For example, a controlled trial of a one-year home-based tailored environmental control & behavioural intervention aiming at indoor allergens (including cockroach) and environmental tobacco smoke was completed in inner-city asthmatic children [40]. Not only did the home-based strategy reduced the cockroach allergen successfully, but it was also associated with reducing cockroach-related asthma morbidity.

Cockroach immunotherapy

Cockroach immunotherapy has the ability to modify the asthma course & provide a prolonged clinical advantage. A limited number of clinical investigations utilising extracts of cockroach allergen revealed improved clinical and immunological parameters [35,41]. The literature supports the effectiveness of allergen immunotherapy for asthma [42], but there are few

published controlled study research that explicitly analyses allergen-specific immunotherapy for subjects allergic to the cockroach.

Rang et al. revealed that subjects receiving an extract of cockroach had reduced medication scores and symptoms, blunted release of in-vitro basophil histamine and a rise in cockroach-specific blocking antibody in a five-year subcutaneous mixed cockroach (American, Oriental & German) immunotherapy trial amongst twenty-eight cockroach sensitive asthmatic subjects after receiving cockroach allergen for 5 years. However, this research's limitation was that even though eleven out of fifteen patients in the active group completed the study, only two out of thirteen received control injections [43]. Another research reported decreased nasal symptoms & an elevation in cockroach specific IgG levels, together with the reduction in levels of serum IL-4, IL-2 as well as IL-4 receptor, after three years of immunotherapy with extract of cockroach [44]. In India, a double-blind, placebo controlled cockroach immunotherapy experiment found that at one year, there was a considerable improvement in bronchial hyper-reactivity & clinical ratings, as well as an elevation in cockroach specific IgG4 [45]. Cockroach immunotherapy may be beneficial, according to these small research.

Wood et al. briefed the outcomes of 4 pilot clinical trials using SLIT (sublingual immunotherapy) & SCIT (subcutaneous immunotherapy) with extract of GC for treating cockroach allergic children and adults [46]. Both cockroach immunotherapy modalities were found to be safe, showing no adverse responses, raising concerns about continuing cockroach immunotherapy research. In terms of levels of IgG4 and inhibiting antibody reactions, subcutaneous immunotherapy was seen to be more immunologically active compared to sublingual immunotherapy. There was a big rise in levels of cockroach specific IgE among placebo and active groups in the adult (n = 54) sublingual immunotherapy trial, as well as a trend toward elevated levels of cockroach specific IgG4 in actively treated participants, but with no indication of functional blocking antibody response. Substantial variations in responses of IgG4, IgG and IgE, were seen between placebo and active groups in the paediatric (n = 99) SLIT research, but no consistent disparities were seen between -low-and high-dose groups. The subcutaneous immunotherapy adult (n = 10) trial discovered that the therapy caused substantial variations from baseline in the levels of cockroach IgG4, IgE, and blocking antibodies [41]. No further clinical studies carried out with extracts of cockroaches have been stated.

However, the absence of standardised extracts as well as the complex patterns of IgE responses to the allergens of cockroach might be obstacles to gain cockroach immunotherapy's full efficiency. Prior to ICAs (Islet cell autoantibodies) immunotherapy studies, a preliminary assessment of relative strengths of 3 extracts of GC which were commercially obtainable showed that they were all of the comparatively low strength [46]. The foremost 2 ICAC (Inner-City Asthma Consortium) investigations of sublingual immunotherapy used a 0.42 ml maintenance dose daily (nearly 3,685 Bioequivalent allergy units, comprising 4.2/50 mcg of Bla g 2/1), and this intermediate dose was compared to a 4-fold higher dose (0.84 ml b.i.d.) and to placebo in the 3rd arm of the last trial [47]. Dose finding research study carried out using standardized extracts for sublingual immunotherapy have identified optimum dose of maintenance for few products, which ranged from 12 µg to128 µg of major allergens per day [48]. Khurana et al. have reported lately on a MAEPA (multiple allergen extract potency assay) developments for simultaneously measuring unidentified as well as identified allergens in extracts of GC, as well as evaluating these extracts' overall effectiveness. Although the role of multiple allergen extract potency assay as a regulatory test for complex allergen extracts has yet to be determined, the research highlights the importance of precise extract comparisons when comparing the findings of numerous studies [49].

In summary, using recombinant or purified natural allergens or derivatives of hypoallergenic allergen seems to have the ability to enhance cockroach immunotherapy's efficacy consistently and surmount the shortcomings of utilizing crude cockroach natural extracts. Although, this method has yet to be implemented in clinical practice.

Conclusion

Cockroach allergy is linked to a higher rate of morbidity as well as increased illness severity in asthma subjects. Clinical findings have been shown to provide conflicting outcomes when it comes to strategies for reducing cockroach allergen exposure in the environment. Immunotherapy with low strength, non-standardized crude extracts from cockroaches have been tried, with satisfactory outcomes although inadequate result reports. Subcutaneous and sublingual cockroach immunotherapyare deemed safe in both children as well as adults. The recombinant allergens' use for the purpose of diagnosis could aid in the selection of the most suitable cockroach allergens for diagnosis as well as treatment in a given area. Finally, recombinant allergens may be employed in clinical studies for cockroach allergy immunotherapy.

Declarations

Conflict of interest: There is no conflict of interest stated by the authors.

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