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KSM Oration

Paediatric Allergic Diseases in Sri Lanka: Unravelling the Uncertain and the Unknown

S. T. Kudagammana

Department of Paediatrics, Faculty of Medicine, University of Peradeniya, Sri Lanka.

Correspondence: S. T. Kudagammana
Department of Paediatrics, Faculty of Medicine, University of Peradeniya, Sri Lanka.
E mail: sanathusara@yahoo.com
ORCiD ID: https://orcid.org/0000-0002-5813-5907

Childhood allergic diseases are a very common clinical problem. There are many children suffering from allergic diseases, but many of them and their parents are perhaps quite unaware that they have the disease. In spite of being a highly prevalent condition with a significant morbidity and mortality, paediatric allergic diseases remain under-diagnosed and under-treated. In many countries of the world, the allergy services have been improved to cater to the needs of the affected but as a country, we in Sri Lanka, seem to be lagging in this regard. Effective treatment options, including immunotherapy and some more recent therapies, are available in many countries but are perhaps not all that freely available for patients in our country.

As a sufferer from allergic rhinitis from quite a young age, my passion for paediatric allergic diseases continued to expand over the years. This oration is an attempt to highlight my contribution towards a concerted effort in trying to understand paediatric allergic diseases and improving the management of those affected.

The common allergic diseases in children include asthma, allergic rhino-conjunctivitis, food allergies, allergic eczema, chronic urticaria and drug allergies. Contrary to earlier postulations that these diseases are separate entities, the current evidence points to them as a single condition with different manifestations. This explains the common clinical scenario of children with asthma having allergic rhinitis and allergic eczema, and *vice versa*. The severity of some allergic diseases can vary from simple urticaria to life threatening severe anaphylaxis. There is also the confounding factor that within any of these given conditions, there is also a point in a rather wide spectrum of the degree of severity to which a given patient may fit into.

Allergic eczema and food allergies are considered to be more common during early childhood and asthma and allergic rhino-conjunctivitis in the older ages. This is explained by the phenomenon of the "*Allergic March*". This term indicates that these diseases are predominant in certain ages of childhood. Accordingly, a child with infantile eczema may tend to go through later periods of predominant allergic asthma and allergic rhinitis with advancing age.

EPIDEMIOLOGY OF ALLERGIC DISEASES

The epidemiology of paediatric allergic diseases cannot be discussed without mentioning the International Study of Asthma and Allergies in Childhood (ISAAC) which is the largest of all epidemiological studies to assess the prevalence and the risk factors of paediatric allergic conditions worldwide.

It is a worldwide collaborative research project ever undertaken, involving more than 100 countries and nearly 2 million children. The main final goal of ISAAC was to try and develop environmental measures and disease monitoring in order to form the basis for future interventions to reduce the burden of allergic and even similar non-allergic diseases, especially for children in the developing countries.

Phase 1 of ISAAC was conducted in 1991 to assess the prevalence and some risk factors for asthma, rhinitis and eczema in many areas of the world. ISAAC Phase 3, a repeat of Phase 1, after at least five years from the initial Phase 1, examined variations in time trends of childhood asthma, rhino-

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conjunctivitis and eczema around the world, and expands the world map of these conditions.

ISAAC Phase 2 involved more intensive studies in a smaller number of selected centres. It began in 1998 and involved 30 centres in 22 countries with 53,383 children participating. Phase 2 enabled internationally standardized comparisons of disease and relevant risk factors using the modules developed by ISAAC collaborators.

Comparing the data gathered from ISAAC Phase 1 study, with the Phase 3 trial data, there is a clear impression that allergic diseases are increasing in prevalence, especially in the countries which had lower prevalence during Phase 1. These included many countries of South Asia. Phase 3 trial also showed that the disparity among the higher and lower prevalence countries was also decreasing.

According to the ISAAC Phase 3 trial the prevalence of wheeze in the past 12 months (current wheeze) ranged from 0.8% in Tibet (China) to 22.6% in Wellington (New Zealand) in the 13–14 year old group and from 2.4% in Jodhpur (India) to 37.6% in Costa Rica in the 6–7 year olds. The prevalence of symptoms of severe asthma, which is clinically more important than above, ranged from 0.1% in Pune (India) to 16% in Costa Rica in the 13–14 year olds and from 0% to 20.3% in the same two centres, in the 6–7 year olds[1].

There is a significant dearth of prevalence data on allergic diseases among children in Sri Lanka. We conducted a study in the year 2010, on a group of 329 school children of 6-7 years of age in Kandy to assess the prevalence of asthma. The translated and validated modified ISAAC questionnaire for 6-7 years was administered to the school children. Those with probable asthma detected by the questionnaire were clinically evaluated by a team of experts including myself, the Principal Investigator. The prevalence of recurrent wheezing was 25%. In addition, 55% of the children studied have had at least one episode of wheezing in the past. All those labelled as having recurrent wheeze, had confirmed asthma on clinical evaluation.

Results of this study were presented at the Kandy Society of Medicine Annual Academic Sessions 2011 as a poster presentation and won the prize for the First Runner-Up Winner Poster of the sessions[2].

The ISAAC Programme was formally closed down in December 2012. The Global Asthma Network (GAN) was initiated in 2012 and it extended and continued the work of ISAAC in the asthma field. The network is a collaborative effort between individuals from ISAAC and the International Union against Tuberculosis and Lung Disease. As a country collaborator of The Global Asthma Network, we conducted a larger study among school children in Kandy in September to November 2018. We used the translated and validated ISAAC questionnaire for the 6-7-year-old and 13-14-year-old children.

The study was funded through a research grant from the University of Peradeniya. We gathered data from 1305 and 1506 children of 6-7 years and 13-14-year age groups respectively in the Kandy District.

According to the findings 14.4 % of the 13-14-year olds and 10.6% of the 6-7-year olds, had wheezing over the past 12 months. In addition, 1.3% and 1.1% of the same age group of children had their sleep disturbed due to wheezing related problems at least one night per week, suggesting its degree of significant severity.

Out of the 13-14-year-old children 12.2 % believed that they have had asthma but only 9.9% of those assessed had their asthma confirmed by a doctor. The two figures for the 6-7-year-old children were 6.2 % and 4.5% respectively.

Of the total 13-14 years old students 12.1% and 4.1 % of 6-7-year-old students, needed to be seen at some time by a doctor urgently for breathing problems. In addition, 9.5% and 3.8 % of the children had at least one day of absence from school due to breathing problems in the same age groups respectively. This signifies the partially controlled or uncontrolled nature of the disease in a significant number of patients.

ASTHMA AND PRE-SCHOOL WHEEZING PHENOTYPES

Asthma is a chronic inflammatory condition of the airways leading to recurrent wheezing, cough and chest tightness in the presence of triggers. These triggers vary from one individual to another. The common triggers include cigarette smoke, domestic cooking hearth smoke, dust mites, cockroaches, moulds, animal dander and change of temperature. The diagnosis of asthma is made mainly on the clinical history. According to GINA guidelines, before starting treatment, the diagnosis of asthma should ideally be confirmed by pulmonary function tests. Spirometry is the commonly used test to demonstrate reversibility of airway obstruction. This needs patient cooperation and it is not possible to use it in small children, especially in those less than 6 years. Impulse

Oscillometry and interrupter technique (ROCC) are pulmonary function tests that can be used in pre-school children, but they are not widely available in our country. These are not dependant on patient compliance and thus are pertinent and very useful tests in this age group.

A commonly used cliché is "all that wheezes is not asthma". This is more so in the pre-school age group. The diagnosis of asthma in the pre-school age group is not easy due to atypical presentations, presence of multiple phenotypes of wheezing and difficulty in performing the commonly available pulmonary function tests. Pre-school wheeze is the result of a complex interaction of genetic and environmental factors starting during foetal life and manifesting in the early years of life. The predictors of the causes and the outcomes will vary when assessed clinically, epidemiologically or when researched with multiple objective measurements. We are increasingly recognizing an evolving syndrome with better information to inform parents and to seek mechanisms which should lead to opportunities for prevention and/or reversibility.

These facts were highlighted in a review article published by me in the Sri Lanka Journal of Medicine titled '*Pre-school wheezing: Is it a form of childhood asthma?*'[3].

There are many pre-school wheezing types which can be classified into phenotypes according to various characteristics, including symptom pattern over time, risk factors and lung function. The phenotypes can be used to prognosticate and help in the management of this group of patients.

This fact that pre-school wheezing is not a homogenous group was brought to the limelight by the Tucson Study. In a seminal report based on the Tucson Children's Respiratory Study, Martinez and colleagues proposed three patterns of wheezing during the first 6 years of life leading to the concept of transient early wheezing in the first 3 years, non-atopic wheezing in the pre-school years and IgE-mediated wheeze or asthma.

This was a ground-breaking study, but the different phenotypes were considered less relevant to clinicians in managing patients. Subsequent to that many studies have attempted to identify different phenotypes during childhood. European Respiratory Society formulated an expert group to devise a clinically relevant phenotypic classification. The recommendations of the group were to categorize recurrent pre-school wheezing conditions into episodic viral wheeze and multi-trigger wheeze. The former includes the wheezers who get episodes only with viral respiratory tract infections and the latter group include the wheezers who get the episodes with other triggers like smoke, dust mite, food allergens, in addition to viral infections[4].

In a study conducted by us on patients admitted to the Teaching Hospital, Peradeniya, with recurrent pre-school wheezing, 66.0% had multi-trigger wheezing and the others (34.0%) had episodic viral wheezing. A significant number of the multi-trigger wheezers were triggered by the so-called "traditional coldfoods".83% fulfilled the criteria for early onset wheezing and the rest (17%) were late onset wheezers. The abstract of the findings were presented at the Annual Academic Sessions of Kandy Society of Medicine in 2015[5].

VIRAL AETIOLOGY OF PRE-SCHOOL WHEEZING

There are many viruses that have been shown to trigger wheezing in children.

They include influenza 1 and 2, respiratory syncytial virus (RSV), *parainfluenza virus* (PIV), human metapneumovirus (hMPV), and *Coronavirus.*

We conducted a study to try and identify the causative viruses in pre-school wheezers in collaboration with Professor Faseeha Noordeen of the Department of Microbiology, University of Peradeniya, during a surge of respiratory tract infections in children. Human metapneumovirus (hMPV), was detected as an important causative agent in addition to other known viruses. Of the 22positive naso-pharyngeal aspirates (NPA)tested for respiratory viral antigens by Immuno-fluorescence Assay (IFA), two were positive for RSV (9.5%), one was positive for influenza A (4.8%) and one was positive for both adenovirus and Para Influenza Virus-2 (4.8%). Of the 22 NPA, 18 (86%) were positive for hMPV. We were the first to identify and report hMPVas a causative agent for pre-school wheezing and as a causative agent for respiratory tract infections in Sri Lanka. A repeat of the study during a standard period without a surge of respiratory tract infections would show the place of hMPV infection in pre-school wheezing.

These results were presented at the Annual Academic Sessions of the Sri Lankan Society of Microbiologists and won the award for the Best Research Paper of the sessions[6]. Subsequently the results were published in *Virus Disease* 2019 entitled A mini outbreak of human metapneumovirus infection with severe acute respiratory symptoms in a

selected group of children who presented to a Teaching Hospital in Sri Lanka[7].

PATHO-PHYSIOLOGY OF ALLERGIC REACTIONS

Allergic reactions have an immunological basis for its manifestations. It could be either IgE mediated (type 1 hypersensitivity reactions) or non-IgE mediated (type 2-4 hypersensitivity reactions).

IgE mediated diseases are characterized by immediate reactions after exposure to the trigger, usually within minutes and may be even up to 2 hours. The common symptoms of these reactions are urticaria, angio-oedema, bronchospasm, stridor, diarrhoea and nasal congestion.

Non-IgE mediated diseases are delayed reactions. The usual clinical manifestations include maculopapular rashes, purpurae, Stevens-Johnson Syndrome, Contact Dermatitis and Toxic Epidermal Necrolysis.

Helper T (Th) cells are a very important group of lymphocytes in immune reactions. When a baby is born, most of the Th cells are of the Th_2 type. This changes to a Th_1 predominance with time when they are exposed to a multitude of antigens. In the "Hygiene Hypothesis" it is postulated that in the genetically predisposed children, cleaner environment with less exposure to the immune challenges, the Th_2 phenotype persists. Th_1 phenotype helps to promote cytotoxic T cells which promote cytotoxic killing and elimination of extraneous agents. Th_2 phenotype promotes stimulation of IgE and eosinophil-mediated inflammation leading to allergy.

A predisposed person exposed to an allergen makes IgE antibodies against it. These IgE antibodies will get attached to the mast cells and subsequent exposure will lead to mast cell degranulation causing an allergic reaction.

AETIOLOGY OF ALLERGIC DISEASES

Why some children develop allergy while others do not, is not clearly understood. Current understanding is that a child, who is genetically predisposed, when exposed to the triggering environmental factors, develops allergic diseases.

Many studies have attempted to evaluate the genetic basis of asthma and allergic diseases. The largest and most comprehensive study of asthma genetics to date was conducted in 2010 by a consortium of more than a hundred centres worldwide. They ran a GWA study (the GABRIEL study)[8], which genotyped 10,365 persons with asthma and 16,110 unaffected persons to test for association between 582,892 single nucleotide polymorphisms and asthma. This large study identified genes on chromosomes 2, 6, 9, 15, 17 and 22 to be associated with asthma. The *ORMDL3* gene, in particular, was associated with childhood-onset, whereas the *HLA-DQ* gene was related to later-onset asthma. Further, the results showed that 38% of all cases of childhood-onset asthma were attributable to a combination of the identified genes.

Family history of asthma and atopy is an important risk factor in asthma and allergic diseases. When both parents have atopy the chance of the child developing asthma reaches 50%.

In a meta-analysis done by a group with W Burke, family history of asthma in one or more first-degree relatives was consistently identified as a risk factor for asthma[9]. In ten studies, sensitivity and predictive value of a positive family history of asthma could be calculated. The sensitivity ranged from 4% to 43%; The positive predictive value ranged from 11% to 37%, and negative predictive value from 86% to 97%.

ENVIRONMENTAL FACTORS AND ALLERGIC DISEASES

Ante-natal and early post-natal exposure to smoke is associated with asthma and allergies. In addition to that, many other factors like exposure to paracetamol and antibiotics have also been shown to be associated with allergic diseases.

According to the ISAAC findings, analyses at an individual level showed that both maternal and paternal smoking was associated with increased risk of asthma symptoms. At an individual level, antibiotic use in the first year of life was also found to be a risk factor. Paracetamol sales were found to be associated with asthma in children and adults. This was explored further in the Phase 3 ISAAC study at an individual level where paracetamol use was found to be a risk factor for wheezing in children and adolescents.

In the Phase 2 Trial, asthma and recurrent wheeze were found to be more common in homes with lower endotoxin levels, and there was a less consistent inverse association of endotoxin levels with allergic sensitization. There were mixed associations

of symptom prevalence with climate, but overall only a little effect.

Exposure to chemicals and pollutants has been debated over the years as a causative factor in these conditions. Some studies have shown that children living in polluted environments have a higher risk of allergies while others have shown results to the contrary. The explanation for studies showing the latter may be due to the chemicals triggering allergies while the former explains the cleaner environments causing more allergies: The Hygiene Hypothesis.

We conducted a study on pre-school children in two estates; one using traditional methods of tea cultivation using agro-chemicals as well as chemical fertilizer, in Talawakelle and the other using organic methods of farming, in Haputale, both for the last 25 years. As you are aware children living in tea estates are very closely exposed to the effects of the environment due to their behaviour and living within the estate itself. Data from 81 pre-school children from the organic estate (Haputale) and 101 pre-school children from the conventional estate (Thalawakelle) were analysed. Recurrent wheezing was noted in 41.2% of children from the organic estate and 59.8% from the conventional estate. The respective percentages for allergic rhinitis were as 37.7% and 82.5% while for eczema they were 17.5% and 20.28%. The difference of prevalence of wheezing and rhinitis were statistically significant at <0.05. We concluded that allergic conditions were more common in pre-school children with environmental exposure to agro-chemicals and chemical fertilizers when compared to that of organic cultivation systems.

The findings of this study were presented as a poster presentation at the International Congress of Paediatric Pulmonology (CIPP) in Krakow, Poland in 2015[10].

The findings were published in the journal of Allergy Asthma and Clinical Immunology in the year 2018 under the title of Environmental exposure to agrochemicals and allergic diseases in preschool children in high grown tea plantations of Sri Lanka[11].

Some of the highlights of the study were published in Sri Lanka Journal of Child Health under *Three Minute Article for Parents* under the title of Exposure to agro-chemicals and occurrence of allergic diseases in children[12].

Being a country with an agriculture-based economy, majority of Sri Lankans are highly involved with agriculture. It is the major income generator in the majority of the population and there are many more families having home gardens to sustain their family economy as well.

We studied the incidence of asthma and allergic diseases in a group of pre-school children growing in standard home gardens (SHG)using a mixture of traditional methods of farming as well as chemicals and the others in improved home gardens (IHG) using improved methods of farming without using chemicals. This study was conducted in a remote village in Nawalapitiya, in the Central Province. This was a multi-disciplinary study which included three specialties. One group studied the plant diversity, second looked at the nutritional intake of the children in the two types of gardens and our group studied the pre-school diseases including allergic diseases. Two groups of families including 19 pre-schoolchildren in each group were followed for a period of 18 months. The results showed that the incidence of allergic diseases among the pre-school children was not different in families with SHG compared to IHG, over the study period.

Findings of our group were presented at the 19thAnnual Scientific Congress of Sri Lanka College of Paediatricians in 2016 as a poster presentation.

The findings of the incidence of allergic diseases were presented at the Annual Academic Sessions of the Kandy Society of Medicine Annual Conference2016[13].

The overall findings of the study were published in the journal *Frontiers in Sustainable Food Systems - Nutrition & Sustainable Diets* under the title "Organized home gardens contribute to micronutrient intakes and dietary diversity of rural households in Sri Lanka"[14].

AIR POLLUTION AND ALLERGIC DISEASES

Air pollution is incriminated as a cause for allergic diseases, mainly childhood asthma. According to ISAAC Phase 2 findings there was no positive association between the centres on air pollution and asthma shown in the Phase One Ecological Studies, with the relationship being slightly inverse. However, in Phase Three findings, high truck traffic exposure in the street where children lived was associated with more asthma symptoms. This suggests that air pollution is not a causative factor for prevalence differences in asthma between populations, but it may be so for individuals within the populations.

Kandy is considered to have relatively polluted air in the country presumably due to its location in a valley. In order to elucidate on that suspicion, we expanded the study using ISAAC tools to school children of 6-7 years and 13-14 years in Anuradhapura. We compared the data of 1715 and 1551children of 6-7 years and 13-14 years of age in Kandy schools with 2276 and 3135 of similar age groups at Anuradhapura. There was no statistically significant difference of wheezing over the last 12 months between 6-7-year-old children but between the children of 13-14 years of age. When we evaluate the statistics of the question evaluating more than one-night disturbance due to breathing problems there was no statistical difference between 6-7-year-old children, but in the children of 13-14 years p=0.003

We also analysed the differences in wheezing over the last 12 months between the students attending Kandy schools with the students attending Wattegama, a sparsely populated rural region. There were 963 students in Kandy Division and 588 in Wattegama Division of 6-7-year olds and 1285 and 472 of 13-14-year-old children in the same divisions respectively.

There was no statistical difference between the 6-7 year old children with wheezing over the last 12 months or children of 13-14 years of age .Though there was no difference in the 6-7 year old children having more than one night per week sleep disturbance ,but in children of 13-14 years of age .This may indicate that the 13-14 year old children in Kandy area are likely to suffer from severe disease compared to their counterparts in Wattegama and Anuradhapura which have cleaner environment.

Management of allergic diseases has taken great strides over the years in many countries. Allergy services have not improved over the very same years in Sri Lanka compared to other specialties. Lack of awareness of such developments among stakeholders, including medical professionals, is a major contributory factor to this problem, along with a very definite lack of resources.

In order to empower the medical fraternity, we organized a conference; The International Conference on Paediatric Allergy and Asthma (ICPAA) in Kandy. The resource persons included our own local experts in allergy and asthma Professor Neelika Malavige, Dr. Rajiv de Silva and Dr. B. J. C. Perera and internationally recognised personalities in the field, Professor Hugo Van Bever from Singapore and Dr. Hithesh Modhi from India, whom I got to know through my collaborations with DAA fraternity. It was a great success, as judged by the feedback and the number of participants who attended the conference. It was an eye opener to many of the attendees.

Next year, we followed it up with an International Workshop on Allergy and Asthma in collaboration with the Sri Lanka College of Paediatricians. This was a joint exercise between us and Asia Pacific Academy of Paediatric Allergy, Respirology & Immunology (APAPARI). We held one workshop in Colombo and one in Kandy. Similar activities to disseminate knowledge are planned for the future.

Allergy testing and pulmonary function tests should be used more often for accurate diagnosis and proper management of patients with allergic diseases. We have started regular spirometry at Teaching Hospital Peradeniya along with skin prick testing. We have provided the services for the nearby hospitals including The Sirimavo Bandaranaike Specialized Children's Hospital (SBSCH) as well. As the premier children's hospital in the region we are working closely with the Paediatric Pulmonologist at the Children's hospital, so that ultimately a larger number of patients will benefit. A complete pulmonary function laboratory capable of assessing lung capacity and diffusion is already developed and two technicians are already trained in India for the purpose. It will be functional very soon for the benefit of the children. We will be able to perform lung function in smaller children using interrupter method as well.

The incidence of allergic diseases in children is high and is increasing in many countries in South-East Asia. Many studies worldwide have shown that there are significant numbers of patients with undiagnosed and uncontrolled disease as well. A screening programme covering the entire nation should be put in place to detect them. Up-to-date techniques of management of allergic diseases should be made available to all our patients in this country. The medical personnel should be empowered with proper clinical and diagnostic tools. Spirometry and skin prick testing should be widely available for the clinicians.

We have highlighted our humble contributions in our efforts towards understanding some of the important aspects of paediatric allergic diseases in relation to our country and its management.

The voyage has just started, perhaps with some small steps; we understand there is a long journey ahead.

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