Timothy Grass Pollen Sensitization in Preschool Asthmatic Egyptian Children

Thesis

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Hadeer Fathy Mohamed Salama

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List of Abbreviations

Abb.	Full term
FPS	Food pollen syndrome
GINA	Global imitative of Asthma
IFN	Interferon
IgE	Immunoglobin E
IUIS	International Union of Immunological Societies
kDa	Kilo Dalton
LTPs	Lipid Transfer Proteins
Pp	Phleum pretense
PPT	Prick Prick test
SPT	Skin prick testing
TGP	Timothy grass pollen
WHO	World health organization

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INTRODUCTION

Asthma is a serious global health problem with a huge social and economic burden ***(Global Initiative of Asthma 2018).*** The most recent revised global estimate of asthma proposes that as many as 334 million people have asthma with increasing burden of disability ***(Braman and Skloot, 2018).***

The increasing prevalence of childhood asthma in the developed world is a cause for great concern; research is currently being carried on aiming to identify possible causes for this occurrence ***(Weinberg, 2000).*** There has been great advancement in medical therapy to prevent the aggravation of asthma symptoms, including improvement in understanding the etiology of asthma, detection of risk factors for asthma exacerbations and encouraging the benefits of writing action plans ***(Akinbami et al., 2011).***

Grass pollens are significant elicitors of IgE-mediated allergic disease in the world and timothy (Phleum pratense) is one of the most important pollens of the family. The assessment of sensitization to grass pollen allergenic molecules could help to develop a better characterization of allergic sensitization in grass pollen allergy in children, which may be different in every patient. It could also enable clinicians to give more specific and effective immunotherapy, based on allergenic molecule sensitization ***(Scaparrotta et al., 2013).***

People who suffer from allergy to pollen after a certain time may develop allergic reactions to certain food. This cross-reactivity in allergy occurs due to the similarity of the pollen and certain food proteins ***(Focak and Solakovic-Focak, 2018).***

Aim of the Work:

This work is aimed to estimate the level of timothy grass sensitization in a group of Egyptian asthmatic children in relation to the level of asthma control. Evaluation of cross reactivity to tomatos and orange is another objective. The ultimate objective is to add information to the map of aeroallergen sensitization in our country.

GRASS POLLEN SENSITIZATION

Grass pollens are one of the most important airborne allergen source worldwide and can elicit severe forms of allergic manifestations, such as asthma ***(Suphioglu et al., 1992; Grote et al., 2000; Taylor et al., 2002; Allergens and Allergen Immunotherapy, 2004; Metz-Favre et al., 2007).***

Grass pollens are important causes of IgE-mediated allergic disease in the world and approximately 40% of allergic patients show IgE reactivity to these allergens ***(Niederberger et al., 1998; Singh and Bhalla, 2003)***

Among the allergic diseases, hay fever is a widespread allergic upper respiratory condition triggered by airborne pollen allergens. Pollen allergen exposure can also exacerbate asthma in susceptible individuals ***(Aalberse, 2000; Scala et al., 2010; Davies, 2014).***

Currently at least 20 grass species such as timothy grass (Phleum pratense) and wheat have been reported to produce pollen proteins associated with the triggering of an IgE response, and the majority of these species are prevalent in temperate climates ***(Andersson and Lidholm, 2003).***

Although documentation is poor, a wide range of aeroallergens has been observed across the African continent. Certain pollens are abundant in Africa, such as olive pollens in North Africa and maize pollen in Zimbabwe ***(El-Gamal et al., 2017).*** In a group of Egyptian children, the most common sensitizing pollen was ryegrass pollen, followed by English

plantain and then Lamb's quarters pollens ***(El-Ghoneimy et al., 2013).*** Timothy grass (Phleum pratense or Pp) is the most important source of grass pollen allergens in northern and central Europe ***(Petersen et al., 1993; Ghunaim et al., 2005).***

Timothy and rye grass pollen contain the majority of IgE epitopes present in most grass species ***(Niederberger et al., 1998).*** For this reason, timothy grass pollen allergens have been characterized in great detail at the molecular level ***(Andersson and Lidholm, 2003).***

Pollens from various grass species contain highly cross-reactive allergens that, depending on initial biochemical studies and on the frequencies of patients' IgE reactivities, have been assigned to certain groups ***(Metz-Favre et al., 2007).***

Allergen specific to timothy:

Figure (1): Timothy grass.

Timothy grass (Phleum pratense or Pp) is the most important source of grass pollen allergens in northern and central Europe ***(Ghunaim et al., 2005; Petersen et al., 1993).***

Common name(s) are timothy grass, Timothy, common cat's tail, While Scientific name is Phleum pretense (Pp), characterized by the cylindrical flower head. Timothy grass grows in clumps that can be as big as 1 meter high, with smooth and hairless leaves that are pale green in color. Young leaves are rolled and become flat and pointed over time. Flowers are located on the end of a stalk and they are densely packed into a cylinder. This cylinder is formed of tiny horned spikelets.

A number of allergen families are reported in grass pollens and/or grains, including β-expansin proteins Phl p 1 from timothy grass **(Table 1)** and Zea m 1 from maize, the lipid-transfer protein (LTP) Zea m 14 from maize, and the gliadin proteins Tri a 19, Tri a 20 and Tri a 21 from wheat ***(Lehto et al., 2003; Goliáš et al., 2013; Pastorello et al., 2013).***

Allergen proteins are found in both pollens and grains and the number of allergen families varies between species. Wheat for example, contains up to 27 allergen families as characterized by the IUIS/WHO guidelines ***(Radauer et al., 2014).***

The most complete set of timothy grass allergens has so far been isolated and cloned from Phleum pratense pollen ***(Hatzler et al., 2012).***

Recombinant timothy grass pollen allergens mimicking the immunologic properties of natural extract–derived allergens have been produced ***(Valenta et al., 1999).*** It has been shown that individual recombinant timothy grass pollen allergens can be used for reliable in vitro and in vivo diagnosis of grass pollen allergy and can replace traditional extracts ***(Niederberger et al., 2001)***.

A clinically successful immunotherapy trial was performed with the major recombinant timothy grass pollen allergens Phl p 1, 2, 5, and 6 has recently been reported ***(Jutel et al., 2005).***

Molecular and biochemical characterization of Pp has revealed several allergen components as rPhl p 1,rPhl p 2, rPhl p 4, rPhl p 5, rPhl p 6, rPhl p 7, rPhl p 11, rPhl p 12 and rPhl p 13, of which rPhl p 1 and rPhl p 5 have been shown to be the "Species Specific Allergens" ***(Mari, 2003)*** the profilin rPhl p 12 ***(Benitez et al., 2001; Ghunaim et al., 2005)*** and the calcium-binding protein rPhl p 7 are the main Cross-Reactive components ***(Scaparrotta et al., 2013),*** the pattern of sensitization to rPhl p 1, rPhl p 5, rPhl p 7 and rPhl p 12 was analyzed in children with asthma and/or rhino conjunctivitis and grass pollen allergy, IgE against to rPhl p 1 were found in 99% (205/207) of patients, to rPhl p 5 in 67% (139/207), to rPhl p 12 in 32% (66/207) and to rPhl p 7 only in 5% (10/207), Sensitization only to "Species Specific" (rPhl p1, rPhl p5) allergenic molecules of Phleum pratense was detected in 65% (135/207) ***(Scaparrotta et al., 2013).***

Structure and features of grass allergens:

Understanding how these allergen encoding genes evolved may be helpful in revealing allergenic properties and for designing future allergy prevention strategies. Understanding the structure of allergens in the Poaceae family will help to uncover common features of allergens and identify targets for manipulation by gene technology ***(Petersen et al., 2001; Andersson and Lidholm, 2003).***

Profilins (Phl p12)

Profilins control the growth of actin microfilaments and cytoskeleton restructuring ***(Sampedro, 2005; Wang et al., 2006).*** Profilins have sequence homologs that are expressed in vegetative tissues and/or reproductive organs, but the function of the putative allergenic profilins remains unknown ***(Müssar et al., 2015).***

In maize, there may be at least two functionally distinct profilin groups, one group inhibiting the hydrolysis of phospholipids and the other group involved in the dynamics of actin filament ***(Kovar et al., 2000).*** A proteomic study found the maize profilin-like putative allergen, Zea m 12, in the pollen coat, suggesting that this protein may play a specific role in this tissue ***(Wu et al., 2015).*** However, not all profilins are allergenic. Very low IgE reactivity was found for Zea m 12, indicating that it may not be a dominant allergen in grasses ***(Petersen et al., 2006; Radauer and Breiteneder, 2006).***

There is fairly low sequence similarity between allergenic and non-allergenic profilins (30–40%), but the allergenic properties have not been well characterized in grasses and the relationship between their function and allergenicity remains unclear ***(Santos and Van Ree, 2011).***

β-Expansins (Phl p1)

Expansins are cell wall-loosening proteins that at least partially mediate the pH-dependent cell wall extension and cell growth. Expansins include two families, α- expansins and β-expansins, and are reported to be involved in modulating a variety of plant developmental events besides cell expansion, including organmorphogenesis, softening of fruits, and grass pollen tube growth ***(Yoo et al., 2003; Sampedro, 2005; Artzi et al., 2016).***

β-Expansins are cell wall expansion proteins expressed in multiple plant tissues. This family of allergens includes the Group 1 grass specific pollen allergens, which are the major allergens in grass pollen that account for the majority of IgE binding in patient sera and to which there is currently no prevention ***(Hirano et al., 2013),*** Although Group 1 allergens are β-expansin proteins in sequence, they exist in multiple isoforms within a single species and may have multiple functions ***(Cosgrove et al., 1997; Sampedro, 2005).***

Expansins promote fruit softening in fruit-producing plants and root hair initiation in Arabidopsis, but these expansins may differ in function from grass specific β-expansin proteins ***(Yoo et al., 2003).*** Many allergenic β-expansin genes