INTRODUCTION

Allergic rhinitis is among the most common chronic disorders of childhood. The incidence of allergic rhinitis has been increasing in the last few decades, in keeping with the rising incidence of atopy worldwide *(Salama, 2003)*.

Allergic rhinitis has a prevalence of up to 40% in children. This can have enormous negative consequences, particularly in children, since it is associated with numerous complications and co-morbidities that have a significant health impact on quality of life. In fact, allergic rhinitis is considered to be a risk factor for asthma *(Brawley et al., 2004)*.

The upper respiratory tract functions as a physical filter, resonator, heat exchanger and humidifier of inhaled air. Failure of any of these functions could clearly alter the homeostasis of the lower respiratory tract *(Salama, 2003)*.

Cigarette smoke is a toxic mixture containing around 4000 different chemicals including a range of carcinogens, irritants, and toxins. It is therefore no surprise that inhaling cigarette smoke, either actively as a cigarette smoker or passively through exposure to

exhaled and side-stream smoke from other smokers, is bad for health *(Britton, 2005)*.

Environmental tobacco smoke (ETS) exposure is associated with atopic and wheezing disorders in preschool children *(Horak et al., 2007)* and involuntary smoking by children has been linked to respiratory infections, middle ear disease, and asthma *(Britton, 2005)*.

Allergic rhinitis is a common cause of nasal obstruction in childhood. Passive smoking tends to increase the symptom of nasal obstruction in children without allergic rhinitis *(De et al., 2005)*.

Clara cell secretory protein (CCSP) is a 16 kDa protein secreted by Clara cells in the lining fluid of airways. CCSP presents several biologic properties, and has been shown to have immune-modulatory and anti-inflammatory activity. It may play a role in controlling inflammation in the airway *(Gioldassi et al., 2004).*

The measurement of airway-specific secretory proteins in serum may detect changes in the number and/or integrity of epithelial secretory cells. This hypothesis is supported by the presence of a decrease in serum levels of CCSP in conditions associated with a

diminution in the number of clara cells and/or in the secretion of CCSP into the lumen of the respiratory tract, such as with tobacco smoking *(Broeckaert et al., 2000).*

The inverse relation between nasal fluid clara cell secretory protein level and symptoms and signs of rhinitis in allergen-challenged patients with intermittent allergic rhinitis may speculate that reduction in anti-inflammatory activity by CCSP may contribute to the pathogenesis of allergic rhinitis *(Benson et al., 2007)*.

AIM OF THE WORK

The aim of this study is to measure the level of clara cell secretory protein as a pneumoprotein biomarker in the serum and nasal lavage fluid in children with allergic rhinitis and to compare these levels in children with history of passive tobacco smoking.

RHINITIS

Introduction:

Rhinitis is an inflammatory disorder of the upper respiratory tract mucosa and is characterized by one or more of the following nasal symptoms: congestion, rhinorrhea (anterior or posterior), sneezing, and itching. Some forms of rhinitis such as atrophic and vasomotor rhinitis are not predominantly inflammatory *(Wallace et al., 2008).*

Rhinitis is a significant cause of widespread morbidity, medical treatment costs, reduced work productivity, and lost school days. Although sometimes mistakenly viewed as a trivial disease, symptoms of rhinitis may significantly affect a patient's quality of life and can be associated with conditions such as fatigue, headache, cognitive impairment, and sleep disturbance *(Wallace et al., 2008).*

Causes of rhinitis:

Dykewicz (2003) classify rhinitis into allergic and non allergic in origin as shown below:

Allergic rhinitis:

- Seasonal.
- Perennial.
- Perennial with seasonal exacerbation.

Non allergic rhinitis:

Structural or mechanical factors:

- Deviated septum.
- Hypertrophic turbinate.
- Adenoid hypertrophy.
- Foreign body.
- Nasal tumour
- Choanal atresia.

Infectious:

- Acute.
- Chronic.

Inflammatory\Immunologic:

- Wegener granulomatosis.
- Sarcoidosis.
- SLE.
- Nasal polyposis.

Physiologic:

- Ciliary dyskinesia.
- Atrophic rhinitis.
- Hormonal induced.

Drug induced:

- Rhinitis medicamentosa.
- Oral contraceptive pills.
- Aspirin.

Reflex induced:

- Gustatory rhinitis.
- Chemical or irritant induced.

Environmental factors:

- Odour.
- Temperature.
- Occupational.

- Non allergic rhinitis with oesinophilia syndrome.
- Vasomotor rhinitis.
- Emotional factors.

Common types of non-allergic rhinitis:

- *Rhinitis medicamentosa:* due to Long term use of topical vaso-constrictors for the nose leading to rebound swelling of the nasal mucosa. Around 30% of patients using vaso-constrictors for long time develop squamous metaplasia *(Tarchalska et al., 2005).*

- *Adenoid hypertrophy:* is considered a common cause of rhinitis in children which leads to persistant nasal obsruction, sleep apnea, and impaired cognitive functions *(Beraldine et al., 2009).*

- *Choanal atresia:* a congenital disorder with partial or complete obliteration of choanal lumen. Usually unilateral. If bilateral, it needs urgent surgical correction *(Mantovani et al., 2009).*

- *Nonallergic rhinitis with eosinophilia syndrome:* presents as congestion and nasal eosinophilia with no obvious allergic source detected on skin testing or RAST. The cause of eosinophilia is unclear. The condition may be associated with non-IgE–mediated asthma, aspirin intolerance, rhinitis with eosinophilia is characterized by eosinophilic infiltration on nasal cytology *(Quillen and Feller, 2006)*.

ALLERGIC RHINITIS

Definitions:

Atopy or allergy is defined as the genetic propensity to generate IgE antibodies against common environmental allergens. Asthma, atopic dermatitis (AD), and rhino-conjunctivitis are the clinical expressions of atopy *(Arshad et al., 2007)*.

Allergic rhinitis is an IgE mediated hyper-sensitivity of the mucous membranes of the nasal airways, eyes, eustachian tubes, middle ears, sinuses and pharynx. This hypersensitivity can be precipitated by exposure to certain allergens, which may be inhalants, digestants, contactants, drugs, infections or endogenous *(Alho et al., 2004).*

Classification:

Allergic rhinitis is classified into two groups, seasonal and perennial. Seasonal allergies, such as those triggered by pollen from ragweed, affect people only during certain times of the year. Perennial allergies, such as those from house dust mites may affect a person year-round *(Rutkowski, 2005).*

A new classification to provide a better description of allergic rhinitis has been proposed by the ARIA as 'intermittent' or 'persistent' rhinitis. The

severity of allergic rhinitis on the other hand can be classified as 'mild' or 'moderate-severe' on the basis of symptoms as well as the quality of life of the patient *(Mullol et al., 2008).*

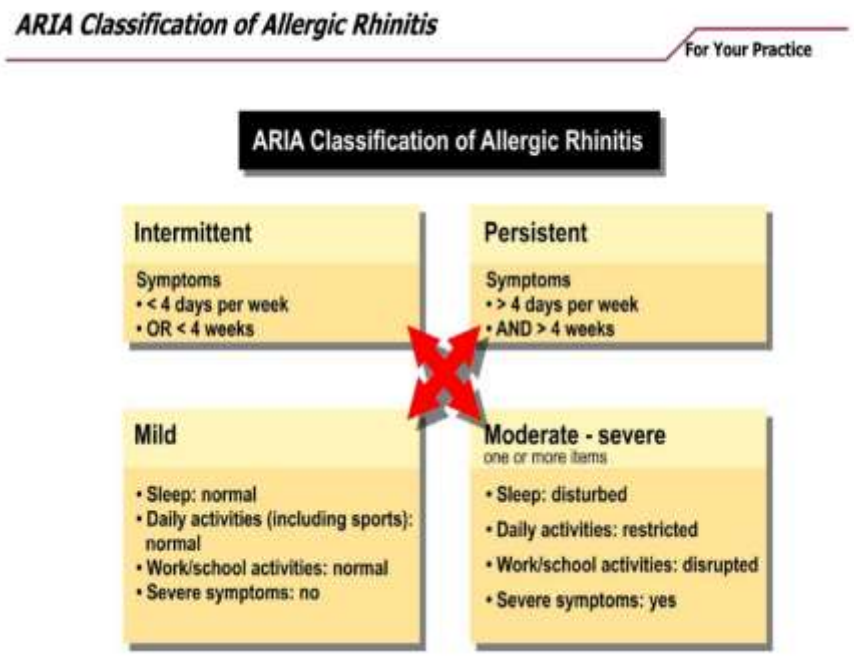

Figure (1): ARIA classification of allergic Rhinitis *(Agache et al., 2009).*

Epidemiology:

Allergic rhinitis is among the most common chronic disorders of childhood. The incidence of allergic rhinitis has been increasing in the last few decades, in keeping with the rising incidence of the atopy worldwide *(Salama, 2003).*

Allergic rhinitis has a prevalence of up to 40% in

children. This can have enormous negative consequences since it is associated with numerous complications and co-morbidities that have a significant health impact on quality of life *(Brawley et al., 2004).*

Prevalence of allergic rhinitis shows a wide variability within and among countries which may be due to genetic, geographic or environmental factors or due to the difference in methods of study *(Nimmagadda, 1999).*

In Egypt, *Georgy et al. (2006)* performed a large study to ascertain the prevalence of allergic rhinitis in Cairo between 11-15 years children and found that 15.3% of the studied group suffering allergic rhinitis.

Etiology:

Allergic responses are adverse, immunologically me-diated reactions to substances that are normally innocuous. These substances are termed allergens and they are often specific proteins that make up an organic structure or organism and renders it allergy producing. Allergens can enter the body and hence

sensitize an individual through inhalation, ingestion, by contact with the skin and by injection *(Sohi and Warner, 2008).*

Allergic rhinitis is atopic genetically inherited disease evoked by exposure to certain environmental allergens:

Genetic factor:

The allergic sensitization that characterizes allergic rhinitis has a strong genetic component. Thus, the chance of developing immunoglobulin E (IgE) / mast cell / T_{H2} lymphocyte immune responses and atopy, in general, is inherited *(Liu and Murphy, 2003).*

Allergic rhinitis is a polygenetic type 1 hypersensitivity disease. More than 20 genes involved in the development of allergic diseases. One of the major genes involved is human MHC HLA class II which regulates the human antigene-specific IgE responses *(Alsuliemani and Walker, 2007).*

Environmental factors:

Allergic rhinitis can be precipitated by exposure to certain allergens which may be inhalants, digestants, contactants, drugs, infections or endogenous *(Alho et al., 2004)*.

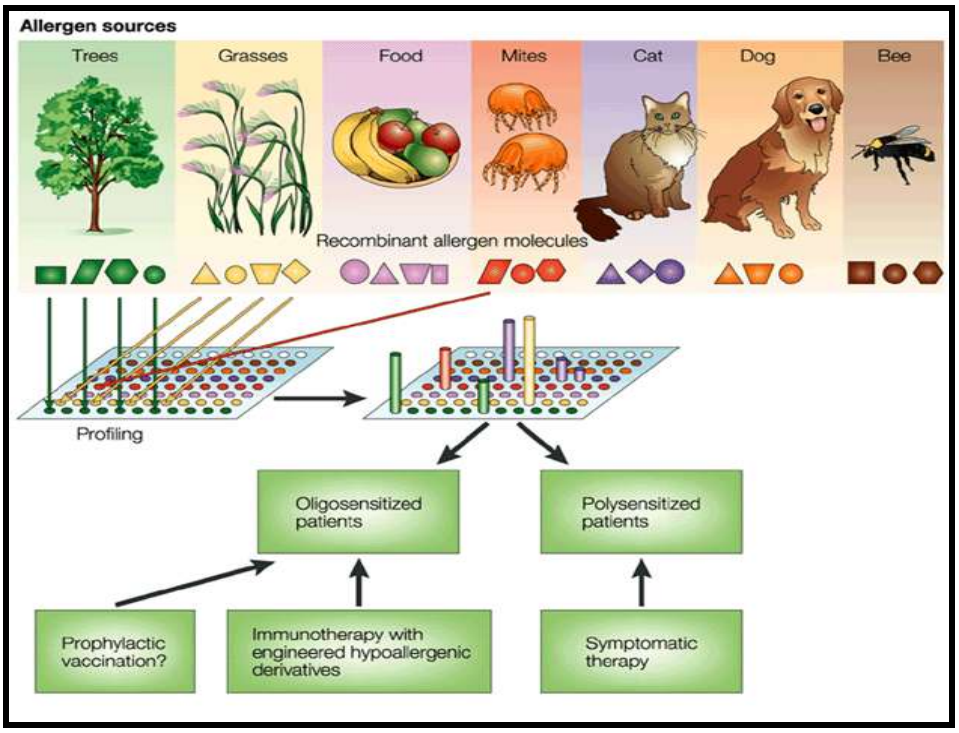

Figure (2): Environmental allergens *(Valenta, 2002).*

Allergens can be found widely in our environment and include common foods and aero-allergens. Aero-allergens, such as the house dust mite, animal dander, various grass and tree pollen as well as fungal mold are the commonest *(Sohi and Warner, 2008).*

Pathophysiology:

Allergic rhinitis is characterized by a two phase allergic reaction, an initial sensitization phase where exposure to allergen results in IgE formation, as well as induction of the humeral response and subsequent clinical phase after repeated antigen exposure. The

clinical phase is further subdivided into early- and late-phase responses *(Lambrecht, 2001)*.

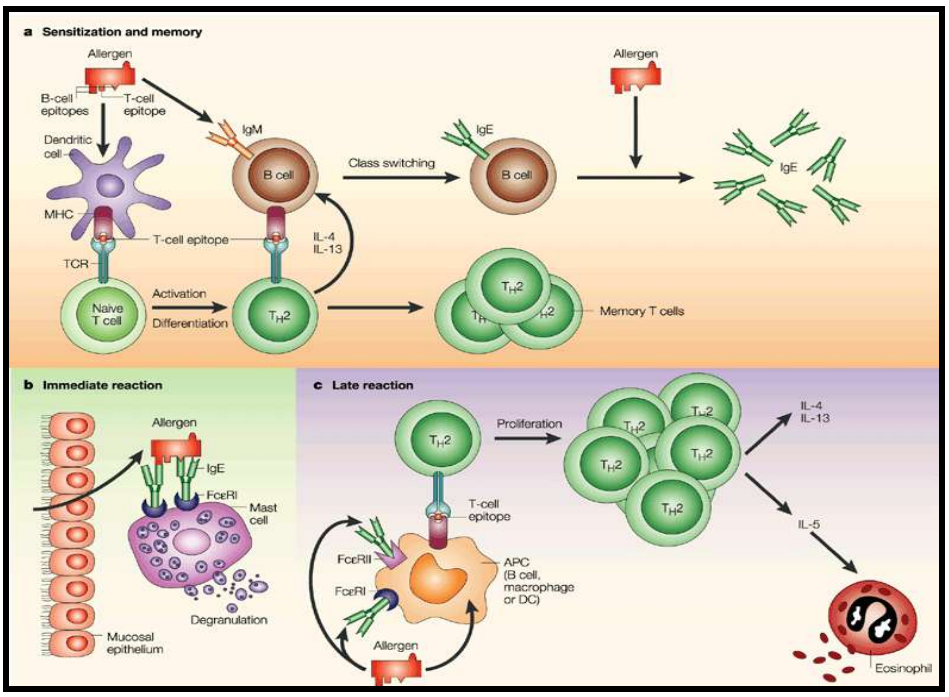

Figure (3): Pathophysiology of allergic rhinitis.

A) Sensitization,

B) Immediate phase.

C) Late phase.

(Valenta, 2002)

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The first step towards generation of a T-helper lymphocyte response is the recognition and uptake of antigen by antigen presenting cells (e.g., dendritic cells, macrophages, B-cells) that have the capacity to digest antigen into short peptides *(Lambrecht, 2001).*

Subsequently, dendritic cells migrate through the sub-mucosa and present the processed antigen to the naive undifferentiated T-helper lymphocytes. Antigen-specific T cells bind the dendritic cell MHC class II-peptide complex with CD4 and this interaction, along with other cell–cell signals, triggers the T cells to differentiate into the B cells which produce T_{H2} cells and activate antigen-specific IgE (*Banchereau et al., 2000).*

Immunoglobulin E (IgE) binds to the FcεR complex on mast cells, basophils, monocytes, and dendritic cells. The molecular interactions responsible for high affinity binding are complex and involve several sites in the $C_{\varepsilon}3$ domain of IgE *(Chang, 2000).*

Circulating antigen specific IgE binds, via the Fc region, to FcεRI receptors on the surface of nasal mast cells and basophils and therby exposes the antigen specific Fab region to the local environment and ready to be activated by further allergen exposure *(Alsuliemani and Walker, 2007).*

The initial exposure and the process of priming the inflammatory cells responsible for executing responses to antigen is referred to as sensitization. Re-exposure to the same allergen on a mucosal surface