INTRODUCTION

Asthma is a common chronic inflammatory disease of the airways characterized with symptoms of wheezing and shortness of breath. The etiology of asthma remains largely unclear. Smoking and environmental factors as well as genetic factors are thought to be its risk factors ***(Wang et al., 2012).***

Asthma is the most common chronic illness in children and is a leading cause of childhood hospitalization and school absenteeism. Asthma is more prevalent in boys in the first years of life, but in adolescents, it predominates among females ***(Herzog and Rundles, 2012).***

Asthma is estimated to affect 300 million people worldwide, with an expected increase to 400 million worldwide by 2025, In a population of children and adolescents ,Bronchial asthma occurs with frequency of 5-10 % . Asthma causes 0.25 million deaths annually and substantial socioeconomic burden around the global. A previous study was done in Cairo, Egypt to ascertain the prevalence of Asthma among children, revealed that the overall prevalence of wheezing in 2009 was 14.7% and of physician-diagnosed asthma was 9.4 % ***(Salama et al., 2010).***

The pre and postnatal development of human immunity is remarkably continuous. The progressive immune response stabilization at the sub-mucosal level during the first year of

life arises from the interface between the host and his microflora. Solid scientific arguments allow hypothesising that immune deviances later in life could be the consequence of an inadequate bacterial pressure on the intestinal mucosa at the early stage ***(Langhendries et al., 2010).***

Helicobacter pylori (*H. pylori*), a helical shaped Gram-negative bacterium, has been shown to infect various areas of stomach and duodenum and has been reported to be associated with gastric cancer risk, The roles of *H. pylori* infection in the development of asthma remain controversial. Recently, increasing studies have been devoted to the association of *H. pylori* infection with asthma risk ***(Wang et al., 2012)***.

Helicobacter pylori prevalence varies depending on the geographic region, age, race, ethnicity and socio-economic status of individual. Helicobacter pylori resides in more than 80% of the stomach of people in the developing world and 40% of those in the western world ***(Shahid, 2012).***

In patients with suspected *H pylori* infection, the following laboratory studies may aid in the diagnosis: H pylori fecal antigen test, urea breath test, stool culture test, ELISA test and Antibiogram test, *H pylori* serology which has High (90%) specificity and sensitivity; is useful for detecting a newly infected patient, but is not a good test for follow up of treated patients ***(Santacroce, 2013)***.

In general, asthma is believed to be caused by exaggerated immunologic responses to antigens in the environment, which are driven by a Th2-mediated immune response. The exogenous infection and microbial substances including *H. pylori* infection may elicit a Th1-mediated immune response, which suppresses Th2 responses. The acquisition of *H. pylori* may be of importance in the induction of regulatory T cells, which could effectively reduce the possibility of allergic asthma ***(Wang et al., 2012).***

AIM OF THE WORK

To assess frequency of *H. pylori* seropositivity in asthmatic children compared to healthy controls, the relation between *H. pylori* IgG seropositivity in asthmatics and asthma severity and control will be also studied.

ASTHMA

Definition:

Asthma is defined as a chronic inflammatory disorder of the lower airways that is associated with airway hyperresponsiveness to a variety of environmental stimuli and reversible airway obstruction, which leads to episodic symptoms of shortness of breath, wheezing and cough, Asthma is associated with significant medical and social morbidity ***(Egan et al., 2013; Brusselle et al., 2013; Holgate, 2013).***

Epidemiology:

The prevalence of childhood asthma in a cohort was 11.0%. Moreover, 22.7% of children had been previously prescribed medication for wheeze or had a lifetime asthma diagnosis ***(Pavilonis et al., 2013)***.

According to World Health Organization (WHO) estimates, 300 million people suffer from asthma and 255 000 people died of asthma in 2005. Asthma is the most common chronic disease among children. Asthma is not just a public health problem for high income countries, it occurs in all countries regardless of level of development. Over 80% of asthma deaths occur in low and lower-middle income countries. Asthma deaths will increase by almost 20% in the next 10 years if urgent action is not taken. Asthma is under-diagnosed and under-treated, creating a substantial burden to individuals and families and possibly restricting individuals' activities for a lifetime ***(Margoushy et al., 2013)***.

Asthma is a major health problem throughout the world, affecting an estimated 315 million persons of all ages. The prevalence of asthma varies widely among countries, ranging from 2% in Vietnam to 27% in Australia ***(To et al., 2012)***.

Asthma occurs more frequently in adults than in children and more frequently in boys than in girls; however, after the teenage years, asthma occurs more frequently in women than in men ***(ALA, 2012)***.

In order to study the prevalence of asthma in Egypt, a large epidemiological study was conducted by ***Deraz, (2008)***, on school children aged 6-15ys. The study was conducted on the governorates which are representative of Cairo and most of the Nile Delta regions. The sudy was condacted in the peroid from 2006 to 2008. The prevalence of asthma in Egyptian children ranged from 10.9% to 18.7% with a mean of 15%.

Asthma Risk Factors:

Most asthma has its origins early in life, suboptimal fetal growth, maternal micronutrient deficiencies, or smoking during pregnancy being associated with impaired infant lung function and later asthma. Both bronchial hyperresponsiveness (BHR) and persistent asthma also have a strong genetic basis independent of atopy. For example, polymorphism of the asthma susceptibility gene ADAM33 on chromosome 20p13 is associated with impaired lung function in infants, increased risk of RSV-induced bronchiolitis, and the later development of BHR ***(Siezen et al., 2009)***.

- **Age and sex:**

Although boys are at substantially higher risk for asthma than girls, the incidence and prevalence of asthma is higher among women of childbearing age than in men. Furthermore, among children less than 10 yrs, the number of hospital admissions is twice as high for boys as for girls ***(Sood, 2012)*.**

Gender-specific prevalence may reflect socio-cultural attitude and possible differences in threshold for seeking medical advice and early frequent antibiotic intake in male children ***(Deraz et al., 2012)***.

Sex hormones have also been implicated in the increased airway hyperresponsiveness noted in adolescent girls ***(Abd-EL-khalek et al., 2003)*.**

- **Breast feeding:**

Breastfeeding is associated with a reduced risk of childhood asthma and asthma-related symptoms**,** The Underlying mechanisms might include immunoglobulin A, cytokines, especially transforming growth factor-β1, and long-chain fatty acids in breast milk that stimulate the infant's immune system ***(Friedman et al., 2005; Giwercman et al., 2010)***.

Factors that modulate the gut microbiota are activated during transit of milk components through the infant gastrointestinal tract. Proteolytic processing of the glycoprotein κ-casein releases glycomacropeptide, which likely acts as a

receptor analog preventing colonization of the gut by pathogens. Similarly, lactoferrin is converted by proteolysis to lactoferricin, a potent antimicrobial ***(Gordon et al., 2012).***

Obesity:

Overweight and, particularly, obese children are at 40-50% increase risk of physician-diagnosed asthma. Moreover, increasing body mass among asthmatic children, was associated with more frequent ambulatory and emergency department visits, as well as increased inhaled and oral corticosteroid use ***(Black et al., 2012; Egan et al., 2013)***.

Obesity could affect asthma in two ways. First, pro-inflammatory adipokines in the circulation of obese individuals could induce airway inflammation or increase its severity, and thus contribute to airway hyperresponsiveness or asthma. Second, the pressure of the increased tissue mass in the chest wall and abdomen has direct mechanical effects on the lungs, which could modify airway hyperresponsiveness or could increase symptoms directly ***(Farah and Salom, 2012)***.

- **Low birth weight:**

Asthma is the most pervasive health problem among very low birth weight children and is also more common among black than white children, partly due to unfavourable environmental exposures ***(McManus, 2012)*.**

Children with very low birth weight had nearly twice the risk of being diagnosed as having asthma compared with moderate low birth weight children and nearly 3 times that of children with normal birth weight. Although the causative factor for asthma development in the very low birth weight child has not been clearly identified, children born weighing less than 1500 g have patterns of reduced pulmonary function similar to those described in children at risk for transient or early-childhood wheezing. Moreover, it is also hypothesized that very low birth weight is a marker for a family or environment vulnerable to the development of asthma ***(Brooks et al., 2001)*.**

- **Environmental Microorganism:**

Reduced exposure to orofecal organisms has been suggested as an explanation for the increasing prevalence of atopy and asthma**.** A broader understanding is that microflora, especially gastrointestinal flora, are important for developing a healthy immune system with resistance to allergic sensitization ***(Ramesy and Celedon, 2005; Risnes et al., 2010)***.

The hygiene hypothesis, although controversia, suggests that microbial exposure in early life enhances postnatal maturation of the immune system that may protect against development of allergic diseases ***(Björkstén, 2009)***.

Microorganisms trigger the innate immune system through pattern-recognition receptors, such as the toll-like receptors. Activation of several toll-like receptors has been found in children exposed to farming environments. Combinations of microbial exposures may activate several signaling pathways downstream of these receptors, with subsequent induction of regulatory T cells. Type 1 helper T cells may be activated and may counterbalance the predominance of type 2 helper T cells that is characteristic of asthma ***(Ege et al., 2011)***.

Interestingly, environmental exposure to a broad range of microorganisms may prevent colonization of the lower airways with harmful bacteria, which has been associated with an increased risk of asthma among children and adults. Balanced colonization of the airways may parallel the beneficial effects of a diverse microbiome at other surfaces, such as the gut and skin ***(Kalliomaki et al., 2008; Costello et al., 2009; Hilty et al., 2010)***.

- **Genetic Factors:**

It is now widely accepted that genetics of asthma and allergic diseases are multi factorial. No single gene or genetic variant can explain all even most of variances in the general population for asthma and allergic diseases ***(Meng and Rosenwasser, 2010).***

Both family-based and twin studies indicate that asthma is a complex genetic disorder. Multiple genetic and environmental factors are also known to modulate the clinical expression of the disease and its associated phenotypes ***(Sleiman et al., 2010).***

Genome-wide association (GWA) studies identify major susceptibility signals for asthma in 1q32, 2p12, 5q12, 5q22, 6q23, 8p21, 9q21, and 17q21 ***(Kabesch, 2010).***

Recently, genetic variants in vitamin D pathway in Egyptian asthmatics have been studied and correlated with severity of asthma ***(Ismial et al., 2013).***

- **Antibiotic use:**

The **"microflora hypothesis"** states that the association between antibiotic use and asthma is caused by the negative impact on the gastrointestinal microbiota ***(Noverr et al., 2005)***.

All antibiotics decrease anaerobic microflora in infants, but use of the broad spectrum cephalosporins leads to the significant suppression of lactobacilli and bifidobacteria, and to the overgrowth of Clostridium difficile ***(Bonnemaison et al., 2003).***

In addition, early childhood penicillin exposure is associated with a relatively high risk for asthma and that amoxicillin, macrolides, cephalosporins, and sulfonamide are also significantly associated with asthma. Asthma is significantly more likely to develop in children receiving antibiotics in a dose-dependent manner with the highest risk is found in children exposed to more than four courses of antibiotics in the first year of life ***(Marra et al., 2009)*.**

Moreover, the adverse effect of antibiotics on asthma risk was particularly strong in children with no parental history of asthma, which should encourage physicians to avoid unnecessary antibiotic use in low-risk children with no genetic predisposition to asthma ***(Risnes et al., 2010)*.**

- **Asthma and atopy:**

Atopy is a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, The allergen triggers an exaggerated immune response, and can aggravate an allergic response on the entire surface of the skin, the conjunctivae, the airways and the digestive tract ***(Yu et al., 2009)*.**

The atopic march has been defined as the natural history of atopic manifestations, characterized by a typical sequence of atopic disease in childhood, generally with Atopic Dermatitis in infancy or early childhood predating the development of other allergic disorders later in childhood, It has been estimated that

approximately one-third of patients with Atopic Dermatitis develop asthma and two-thirds develop allergic rhinitis ***(Spergel et al., 2010)*** Furthermore, it has been shown that the atopic march can occur at any age, not just in childhood ***(Burgess et al., 2008)*.**

Potential biological mechanisms for the atopic march revolves around that the immunology and pathophysiology of atopic dermatitis, allergic rhinitis, and asthma is similar, the immune cells migrate through lymphatic (dendritic cells, APCs, naïve and activated lymphocytes) and vascular (lymphocytes, macrophages, eosinophils and neutrophils) systems and carry with them what they have learned or been "**pre-programmed**" to do. Exposure to allergens elsewhere (after sensitization) promotes inflammatory response in that organ (skin, eyes, nose, lungs or gut) that reflects the allergic condition ***(Leynaert et al., 2004)***.

Interestingly, the hygiene hypothesis states that early training of the immune system occurs through contact with pathogenic microbes, or alternatively through effects of commensal microflora (or both), thus strengthening the Th1 arm of the defense. In the Western lifestyle, such encounters would be less common, and in urbanized environments a shift toward Th2 responses would lead to the development of atopy ***(Frei et al., 2012; Heederik and Von Mutius, 2012; Hanski et al., 2012)***.

- **Asthma Phenotypes:**

1- Transient infant wheezing:

Most children who wheeze during infancy do not wheeze after the age of 3 years. These "transient wheezers" do not have a family history of asthma or any marker of atopic diathesis, but are characterized by impaired lung function at birth ***(Lau et al., 2003).***

2- Non atopic wheezing of the toddler and early school years:

A second group of children continues to wheeze beyond the third year of life. Approximately 40% of these children are non atopic, and often these children have a history of viral lower respiratory tract infection early in life, in particular, respiratory syncytial virus ***(Bisgaard et al., 2003).***

3- Persistent IgE-mediated wheezing/asthma:

A third group of children will go on to have persistent, chronic asthma. This persistent wheezing phenotype was associated with high levels of atopy, bronchial responsiveness, and impaired lung function, a variety of risk factors for persistent IgE-mediated wheezing are Identified, of which genetic factors (atopy, parental history of asthma, male gender) and early allergic sensitization (house dust mite, cockroach) are the most important ***(Lemanske et al., 2002).***

Of interest, certain early exposures seem to decrease the risk for persistent wheezing ***(Platts–Mills, 2002)***. Early exposure to farm animals has been shown to have a protective effect against both allergic sensitization and asthma. Recent evidence suggests that this effect might be mediated by exposure to bacterial endotoxins ***(Braun–Fahrlander et al., 2002).*** Also, growing up in a house with pets or dogs appears to decrease the risk of allergic sensitization and wheeze ***(Celedon et al., 2002)***, independent of the effects of endotoxin ***(Litonjua et al., 2002)***. Systemic bacterial or parasitic infections ***(Yazdanbakhsh et al., 2002)*** in early life might protect against the development of atopy and asthma as well. Certain infections, mainly food-borne and orofecal, are associated with a lower risk of asthma and common allergies ,and neonatal bacilli calmette-guerin (BCG) vaccination is associated with a reduced prevalence of allergy and asthma in children with an inherited predisposition to allergic diseases ***(Marks et al., 2003).***

4- Late-onset childhood asthma:

Late-onset childhood asthma is the least well-described subtype of childhood asthma ***(De Marco et al., 2002)***.

An asthma phenotype occurring during or after puberty, affecting mainly women and with a low remission rate. A higher prevalence of bronchial hyperresponsiveness among postpubertal compared with prepubertal girls was confirmed, and also in these children atopy is the major determinant of bronchial hyperresponsiveness ***(Ernst et al., 2002).***