Introduction

Asthma is a serious global health problem. People of all ages in countries throughout the world are affected by this chronic airway disorder that, when uncontrolled, can place severe limits on daily life and is sometimes fatal. The prevalence of asthma is increasing in most countries, especially among children. Asthma is a significant burden, not only in terms of health care costs but also of lost productivity and reduced participation in family life ***(GINA, 2008).***

Asthma is a complex disease physiologically characterized by shortness of breath, coughing, and wheezing. Asthma generally develops in childhood and is associated with sensitization of the airways to aeroallergens such as house dust mites, cockroaches, animal dander, fungi, and pollens ***(Holgate, 2011).*** In response to a variety of stimuli, the airways become more sensitive leading to bronchial hyperresponsiveness ***(Kang et al., 2012).*** Consequently, in a process known as bronchoconstriction, airways become narrower, impeding the normal airflow into and out of the lungs ***(WHO, 2011).***

Dendritic cells (DC) are unique professional antigen presenting cells that coordinate both innate and adaptive arms of the immune system ***(Bancheread et al., 2000).*** The majority of pulmonary DCs are derived from a pool of DCs that traffic from peripheral blood rapidly in response to antigen ***(Farrel et al., 2007).***

Dendritic cells (DCs) process and display antigens and therefore have a crucial role in determining T lymphocyte responses ***(Lambrecht and Hammad, 2009).*** Pulmonary DCs, which continually sample inhaled antigens directly from the airway, are thought to play an important role in the development and persistence of asthma ***(GINA, 2010).***

DCs are also known to display marked heterogeneity, and a commonly employed sub-classification is into conventional (also known as myeloid) and plasmacytoid cells. Conventional DCs (cDCs) have a crucial role in the development of Th2 responses and allergic airways inflammation, while plasmacytoid DCs (pDCs) have a role in response to viral infections, development of tolerance and control of allergic airways inflammation ***(Lambrecht and Hammad, 2009).***

Cigarette smoking is known to impact on a number of allergic and autoimmune diseases ***(Stampfli and Anderson, 2009).*** In vitro research has demonstrated that cigarette smoke alters DC function with effects on the development of Th2 responses ***(Vasallo, 2005).***

Aim of the Study

The aim of this work was to assess peripheral blood DC profiles in Children with different clinical and functional grades of asthma.

Chapter 1

Childhood Bronchial Asthma

Definition

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. This chronic inflammation is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with wide spread but variable airflow obstruction that is often reversible either spontaneously or with treatment ***(GINA, 2011).***

Epidemiology

1. Prevalence:

Asthma is the most common disease in children with a prevalence varying between countries ***(Baiz and Annesi, 2012).***

Several studies have suggested a similar prevalence of asthma among children and adult populations; however, extensive variability has been found depending on multiple factors that include geographic differences and socioeconomic status ***(GINA 2010).***

According to World Health Organization (WHO) Estimates, 235 million people worldwide currently have asthma ***(WHO, 2010).*** By the year 2025, as more communities adopt a westernized lifestyle and become urbanized, it is expected that there will be 400 million people worldwide with asthma ***(Moorman et al., 2011).***

In US, recent reports from national surveys showed that the prevalence of asthma continues to rise in both children and adults, and in all racial and ethnic groups ***(Moorman et al., 2011).*** Among children (<18 years old), the prevalence of asthma increased from 8.7% in 2001 to 9.6% in 2009 ***(CDC, 2011).***

During the second half of the 20th century, the rise in asthma from 1960 to 2000 coincided with truly remarkable changes in lifestyle. However, the changes in hygiene that appears to be sufficient to induce a western model of asthma in Africa or Costa Rica had occurred in London, Berlin and New York almost 40 years earlier (i.e. by 1920) ***(Sordillo et al., 2011).***

In Egypt:

It is one of the commonest causes of emergency and hospital admission in Egypt as the prevalence of asthma among Egyptian children aged 3-15 years was estimated to be 15-16 % and one in four children with asthma fails to attend school regularly because of poor asthma control ***(Tag eldin, 2007).***

Fahim et al. (2006) reported that the prevalence of physician-diagnosed ashma in Cairo was 9.4% and there is a high prevalence, increased severity of asthma in children of low socioeconomic group. The prevalence rate of asthma in Nile delta regions 7.7% (8% in rural and 7% in urban) ***(Magdy et al., 2009).***

Abdel Latief (2000) reported that the prevalence of pediatric asthma among 2321 secondary school students (13 to 20 years old) in four randomly selecte.d districts (Misr El-Gedida, Helwan, Shoubra, Abbassia) is 5.6%.The prevalence of ashma among Egyptian children aged 3-15 years was estimated to be 8.2%.Of major concern is the annual increase in mortality ***(Hossny et al., 2009).***

In order to study the recent prevalence of asthma in Egypt, a large epidemiological study in school children aged 6-15 years from 2006-2008 in the following governorate which representive of Cairo and most of Nile delta regions. The prevalence rate of asthma in Egyptian school children ranged from 10.9% to 18.7% with mean 15.1 % ***(Deraz et al., 2008).***

2. Race:

It has been shown that African–Americans tend to have more severe acute asthma episodes than white patients, and have greater utilization of emergency healthcare ***(Wechsler et al., 2011).***

3. Age:

In 2006, the highest current prevalence rate was seen in those 5-17 years of age (106.3 per 1000 population), with rates decreasing with age. Overall, the rate in those under 18 (92.8 per 1000) was much greater than those over 18 (72.4 per 1000). In most children, asthma develops before they are aged 5 years, and, in more than half, asthma develops before they are aged 3 ***(ALA, 2008).***

4. Sex:

Fouda et al. (2008) and Deraz et al. (2011) reported that there was gender difference seen in asthma with more males affected by asthma prior to adolescence and more females during adolescent and adulthood.

Male sex is a risk factor for asthma in pre-pubertal children. Female sex is a risk factor for the persistence of asthma in the transition from childhood to adulthood ***(Toelle et al., 2004).*** Boys with asthma are more likely to "grow out" of their asthma during adolescence than girls ***(Castro et al., 2000)***.

Asthma predominates in boys during childhood with male to female ratio 2:1 until puberty and when the ratio becomes 1:1 the symptoms more are decreased in boys by adolescence ***(El Seify, 2010); (Shaheen, 2003)*** attributed this sex difference to hormonal factor.

5. *Mortality and morbidity associated with asthma:*

Mortality from asthma is most common in low to middle income countries ***(WHO, 2007).*** Among children asthma deaths are rare in 2003, 195 children died from asthma, or 0.3 deaths per 100.000 children compared to 1.4 deaths per 100.000 adults ***(NCHS, 2006).***

Asthma Comorbidities

Other conditions may co-exist with asthma, and continuing respiratory symptoms may be wrongly attributed to asthma alone. These children may be difficult to treat. The most common comorbidities are chronic rhinosinusitis, gastro-oesophageal reflux and obesity ***(Hedlen et al., 2012)***.

1. *Rhinitis and Rhinosinusitis*

The relationship between the nose and the lung is complex and it has been reviewed in several studies ***(Bousquet et al., 2010).*** The prevalence of allergic rhinitis in children with asthma was 64.3% and that of asthma in children with allergic rhinitis was 21.6% ***(Kim et al., 2013)***.

Chawes et al. (2010) reported that children with allergic and non-allergic rhinitis have a similar risk of asthma. It is still unclear whether sinusitis worsens asthma, or whether both are manifestations of the same underlying disease process. However, the observation that patients with severe asthma report clinical symptoms of rhinoconjunctivitis more often than those with controlled asthma was found in a Swedish study ***(Konradsen et al., 2011).***

The fact that untreated rhinitis contributes to reduced symptom control in asthmatic children has become increasingly evident ***(De Groot et al., 2012).*** In children, chronic rhinosinusitis is possibly also an underestimated disease ***(Hastan et al., 2011).***

2. Gastro-oesophageal reflux

20–80% of children with chronic respiratory disease have gastro-oesophageal reflux ***(Thakkar et al., 2010)***. The results of trials of anti-reflux therapy are often disappointing especially in older children, but an empirical trial is reasonable in younger children if the history is suggestive ***(Holbrook et al., 2012).*** Although, Reflux oesophagitis it is difficult to be oriented by younger children, it was noticed as a risk factor in 29.1% of patients. There was a highly statistical significant difference between Cases and controls group (p-value <0.001) ***(Shaaban et al., 2012).***

3. Vocal cord dysfunction

Some breathing problems can be confused with asthma. In particular, vocal cord dysfunction may co-exist with asthma and may be a differential diagnosis, leading to inappropriate asthma treatment ***(Hedlen et al., 2012). Low et al. (2011)*** reported a noninvasive method for quantification of laryngeal movement by using computed tomography (CT) of the larynx. A 320-slice CT was used to monitor laryngeal behaviour. A specific pattern of laryngeal dysfunction was

demonstrated, which was observed in patients with difficult-to-treat asthma ***(Ayres and Mansur, 2011).***

4.Obesity

A recent study from Australia reported that obesity is a determinant of asthma control independent of inflammation, lung function, and airway hyperresponsiveness ***(Farah et al., 2011)***. High body mass index (BMI) has been associated with the increased incidence and prevalence of asthma, asthma severity, reduced responses to standard asthma medications, persistent symptoms and poorly controlled disease ***(De Groot et al., 2010).*** BMI was inversely correlated with most of pulmonary function abnormalities ***(El-Baz et al., 2009).*** suggesting a specific phenotype of asthma in obese individuals ***(Mahadev et al., 2012).***

Obesity increases the risk of asthma in both sexes and in different ethnic groups. Several factors have been proposed, including obstruction of upper airways flows, gastro esophageal reflux, inconsistent breathing from sleep-disorders, and the relationship between physical and sedentary activity, genetics and the state of low-grade systemic inflammation through obesity ***(Holguin, 2012).*** Baseline pulmonary function tests and regular assessment are recommended for early discovery of bronchial obstruction in the obese children ***(Kamel, 2011).***

A recent study showed that increase eosinophilic activity (chemotaxis and adhesion) in a topic asthmatic obese child ***(Grotta et al., 2013)***. Obesity also impairs lymphatic

fluid transport and migration of DCs to the peripheral lymph nodes ***(Weitman et al., 2013)***.

5. *Vitamin D deficiency and asthma:*

Beside importance for bone health, vitamin D plays an important role in adequate function of both the innate and adaptive immune systems including development of dendritic cells and regulatory T lymphocytes ***(Paul et al., 2012).*** Recent reports suggest that vitamin D might play a role in the recent increase in allergic disease ***(Osborne et al., 2012).***

The impact of low serum levels of vitamin D in relation to lung disease and to asthma, in particular, is a subject of discussion. The study by Gupta *et al.* showed that increased airway remodelling, as measured by smooth muscle in biopsies, correlated to levels of vitamin D in children with severe asthma. This relationship did not exist for children with moderate asthma and in healthy controls Risk of exacerbation was increased in children with low levels of vitamin D ***(Gupta et al., 2011),*** In addition; ***Chinellato et al. (2011)*** reported an association between exercise-induced asthma and vitamin D levels. (Fig.1). ***Ismail et al. (2013)*** recogneized some genetic variations in vitamine D pathway in the Egyptian asthmatic childerns.

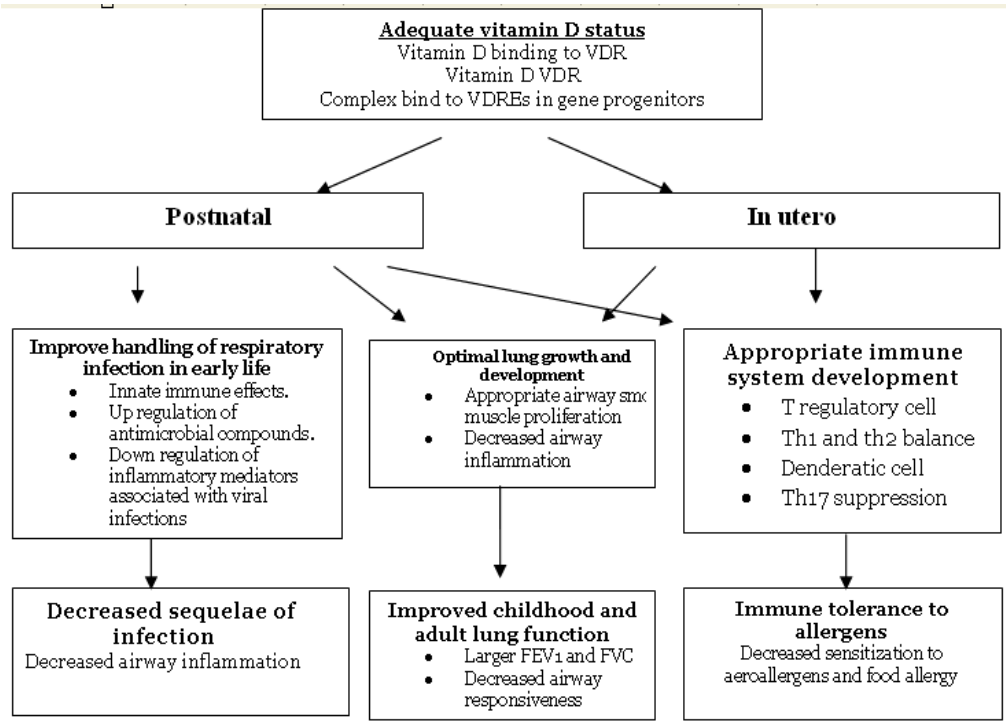

Fig. (1): Mechanisms of vitamin D in asthma and allergy development ***(Litonjua, 2010)***

Factors influencing the development and expression of asthma

Factors that influence the risk of asthma (table 1) can be divided into those that cause the development of asthma and those that trigger asthma symptoms; some do both. The former include host factors (which are primarily Genetic) and the latter are usually environmental factors ***(Lemanske and Busse, 2011).***

The mechanisms which influence the development and expression of asthma are complex and interactive. For example, genes likely interact both with other genes and with environmental factors to determine asthma susceptibility ***(Ober and Vercelli, 2011).***

Although the cause of childhood asthma has not been definitely determined, current research includes a combination of environmental respiratory exposures, such as inhaled allergens, respiratory viral infections, air pollutants, and genetic vulnerabilities ***(Cobanoglu et al., 2013).***

Table (1): Factors influencing the development and expression of asthma

1- HOST FACTORS:
a-Genetic, e.g.
• Genes pre-disposing to atopy
• Genes pre-disposing to airway hyperresponsiveness
b-Obesity
c- Sex
11-ENVIRONMENTAL FACTORS:
a- Allergens
• Indoor: Domestic mites, furred animals (dogs, cats, mice), cockroach allergen, fungi, molds, yeasts
• Outdoor: Pollens, fungi, molds, yeasts
b- Infections (predominantly viral)
c- Occupational sensitizers
d- Tobacco smoke
• Passive smoking
• Active smoking
e- Outdoor/Indoor Air Pollution
f- Diet

(GINA, 2011)

1. Host Factors:

A- Genetic:

Asthma is considered a complex genetic disease involving the interaction of multiple genes with each other (gene- gene interactions) and the environment (gene-environment interactions), including; infection (viral, bacterial), allergen

exposure, pollution and smoking ***(Ober and Vercelli, 2011).*** More than 100 genes have been implied in asthma susceptibility across populations ***(Zhang et al., 2013).***

It remains largely unknown how these genes predispose individuals to specific clinical phenotypes that contribute to asthma. However, it is anticipated that polymorphic variation within these genes and relevant pathways will define subgroups and have pharmacogenetic effects on drugs designed to target these pathways (tab. 2) ***(Portelli and Sayers, 2012).***

Mikhaylova et al. (2013) demonstrated that neonates at-risk of asthma are born with substantial genome-wide DNA methylation changes in their DCs due to maternal allergy. Based on the paradigm that allergen sensitization in responsive subjects leads to genome-wide changes in the transcription of immune cells as they activate.

Table (2): Asthma susceptibility genes

Gene \region	Chromosome	Function	Ref.
IL6R	1q21	Regulatory T-cell function, T-cell differentiation	***(Ferreira et al., 2011)***
DENND1B	1q31	Memory T cell functions	***(Sleiman et al., 2010)***
IL1RL1	2q11	IL-33 receptor, recruitment/ activation of inflammatory cells	***(Moffatt et al., 2010)***
PDE4D	5q12	Modulates cAMP, role in cell signaling, inflammation and airway smooth muscle function	***(Himes et al., 2009)***
TSLP	5q22	Activates dendritic cells, role in Th2 immune responses	***(Moffatt et al., 2010)***
HLA-DQ	6p21	Cell membrane alloantigens, T-cell responses	***(Moffatt et al., 2010)***
IL-33	9p24	Produced by airway structural cells, recruitment and activation of inflammatory cells	***(Moffatt et al., 2010)***
LRRC32	11q13	Regulatory T-cell function	***(Ferreira et al., 2011)***
SMAD3	15q22	TGFβ signalling intermediate, fibrosis	***(Moffatt et al., 2010)***
ORMDL3/GSDMB	17q21	Sphingolipid synthesis (ORMDL3), cell apoptosis? (GSDMB)	***(Moffatt et al., 2010)***
IL2RB	22q12	Binds IL-2/IL-15, lymphoid cell differentiation	***(Moffatt et al., 2010)***

(Portelli and Sayers, 2012)