بسم الله الرحمن الرحيم

" أقرأ باسم ربك الـــذي خلـــق,خلـــق
الأنسان من علق ,أقرأ وربك الأكرم ,
الذي علم بالقلم,علم الأنسان مالم يعلم"

صدق الله العظيم

العلق اية 3:1

THYROID FUNCTION IN RELATION TO ACUTE SEVERE ASTHMA

Thesis

Submitted for fulfillment of

M.Sc degree of ***CHEST DISEASES & TUBERCULOSIS***

BY

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ABSTRACT

A link has been noticed between thyroid disease and asthma; the most frequent reports have been of worsening of established asthma with the onset of hyperthyroidism, with subsequent improvement of the asthma when the euthyroid state is restored.

The aim of this work was to determine whether systematic analysis of thyroid function is a useful requirement for all patients with difficult-to-manage asthma? The study was conducted in Chest Diseases Department of Kasr El Aini Hospital, Cairo University in the period from November 2006 to April 2007.

All cases were subjected to

1- *History taking*
2- *Full clinical examination both general and local : of chest, cardiovascular system, central nervous system, abdominal, skin, skeletal, genital, ophthalmic systems. Hypertensive and Diabetic patients had been excluded.*
3- *Plain chest X-ray (postroanterior and lateral view)*
4- *Free T3, T4 and TSH were measured among 20 patients having acute severe asthma every 12 hours for 48 hours.*

Another sample was taken after controlling the attack.

It was concluded that there is no increase or decrease in the thyroid hormones (T3, T4, and TSH) levels before and after the asthma attack.

KEY WORDS

Acute severe asthma
Thyroid hormones

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List of abbreviations

AFAM33	adisintegrin and metalloprotease domain
AHR	airway hyperreactivity
ECF-A	easinophil chemotactic factor of anaphylaxis
EGF	epidermal growth factor
GM-CSF	granulocyte-macrophage colony stimulating factor
IgE	Immunoglobulin E
IL4	interleuken -4
INF gamma	interferon gamma
MMPs	matrix metalloproteinases
NCF	neutrophil chemotactic factor
PGD2	prostaglandin D2
RCMB	respiratory cell and molecular biology
SCCA -1	squamous cell carcinoma antigen-1
STAT factor	signal transduction-activated transcription factor
T (reg)	T regulatory cell
TGF-B	transforming growth factor beta
TIMPs	tissue inhibitors of metalloproteinases
VCAM-1	vascular cell adhesion molecul-1

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INTRODUCTION

The word *asthma* is derived from the Greek word *aazein*, meaning "sharp breath." Hippocrates was the first to use it in reference to the medical condition; Hippocrates thought that the spasms associated with asthma.

Six centuries later, Galen wrote much about asthma, noting that it was caused by partial or complete bronchial obstruction. The use of bronchodilators started in 1901, but it was not until the 1960s that the inflammatory component of asthma was recognized, and anti-inflammatory medications were added to the regimen

(Anthony and Douglas Seaton, 2004)

- **Asthma** is a chronic disease that affects the airways, in which the airways constrict, become inflamed, and are lined with excessive amounts of mucus, often in response to one or more "triggers," such as exposure to an environmental stimulant (or allergen), cold air, exercise , or emotional stress. In children, the most common triggers are viral illnesses such as those that cause the common cold. This airway narrowing causes symptoms such as wheezing, shortness of breath, chest tightness, and coughing, which respond to bronchodilators. Between episodes, most patients feel fine.
  (GINA Guide lines, 2006)

- **Acute severe asthma:** is a medical emergency in which asthma symptoms are refractory to initial bronchodilator therapy in the emergency department. Patients report chest tightness, rapidly progressive shortness of breath, dry cough, and wheezing. Typically, patients present a few days after the onset of a viral respiratory illness, following exposure to a potent allergen or irritant, or after exercise in a cold environment. Frequently, patients have underused or have been underprescribed anti-inflammatory therapy. Illicit drug use may play a role in poor

adherence to anti-inflammatory therapy. Patients may have increased their beta-agonist intake (either inhaled or nebulized) to as often as every few minutes. (Allergy Asthma Proc ,2001)

- **Thyroid:** Thyroid is known as the hormone factory of the body, as it manufactures a number of hormones for the body.

  T3 and T4 are the major hormones amongst them. Among various other things these hormones control the body's metabolism and energy levels. Body fails to function properly in case of excess or lack of these hormones. While lack of these hormones make the body sluggish and slow an excess of these make the person hyper active sending the body in an overdrive.

  (Luong and Nguyen, 2000)

- **Thyroid function and asthma:** Hyperthyroidism and asthma, and the underlying factors potentially contributing to their conditions. Many researches suggest that asthma may develop in a susceptible individual with hyperthyroidism and so many possible factors may be a contributory reason in exacerbating wheezing" (White et al.,1999)

AIM OF THE WORK

Determine whether systematic analysis of thyroid function is useful for all patients with difficult-to-manage asthma.

DESCRIPTIVE DEFINITION

Definition of asthma

According to the global Initiative for Asthma (GINA guidelines) 2006

Asthma is a chronic inflammatory disorder of the airways in which many cells play a role, in particular mast cells, eosinophils and T lymphocytes. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and/or in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible either spontaneously or with treatment. This inflammation also causes an associated increase in airway responsiveness to a variety of stimuli.

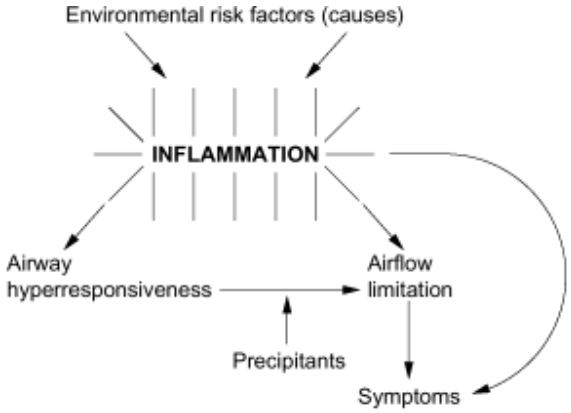

Figure 1 . Mechanisms Underlying the Definition of Asthma (Stephen and Holgate, 2006)

Allergic asthma:

Is the basic term for asthma mediated by immunological mechanisms? When there is evidence of IgE-mediated mechanisms the term IgE-mediated asthma is recommended. IgE antibodies can initiate both an immediate and a late asthmatic reaction. However, as in other allergic disorders, T-cell associated reactions seem to be of importance in the late and delayed reactions. (Milgrom. 2003)

***Non-Allergic Asthma*:**

This is the preferred term for non-immunological types of asthma. It is recommended that the old terminologies, extrinsic, intrinsic, exogenous, and endogenous asthma should no longer be used to differentiate between the allergic and non-allergic sub-groups of asthma. (Milgrom. 2003)

Historical background

History of Asthma

- The word *asthma* is derived from the Greek word *aazein*, meaning "sharp breath." The word first appeared in Homer's *Iliad*; Hippocrates was the first to use it in reference to the medical condition. Hippocrates thought that the spasms associated with asthma were more likely to occur in tailors, anglers, and metalworkers. Six centuries later, Galen wrote much about asthma, noting that it was caused by partial or complete bronchial obstruction
  (Guilbert and Krawiec , 2003)
- In the 17th century, Bernardino Ramazzini noted a connection between asthma and organic dust. The use of bronchodilators started in 1901, at 1960 the inflammatory component of asthma was recognized, and anti-inflammatory medications were added to the regimen. . (Guilbert and Krawiec ,2003)

Risk factors

Common risk factors and ways to avoid them are illustrated below:

(Bernstein et al., 1999)

Risk Factor	Avoiding Action
Domestic dust & mite allergens	Wash bed linen weekly, keep pillows and mattress in air-tight covers, and replace carpets with linoleum etc, use vinyl, leather or wood furniture. Vacuum with a filter.
Tobacco smoke	Avoid all tobacco smoke

Allergens from furry animals	Ban animals from home, or at least bedroom.
Cockroach allergen	Clean suspect areas regularly, and spray.
Outdoor pollens and molds	Windows and doors shut when counts are high
Indoor mold	Reduce dampness in the home.
Physical activity	Don't avoid exercise - use an inhaler first!
Drugs	No beta-blockers, aspirin, or NSAIDs if these cause symptoms.

The Complexity of Genetics

- One thing is certain about genetics and asthma. There is no one "asthma gene". Several genes interact and cause susceptibility to asthma. Keep in mind, that one may have the genes to predispose him/her to asthma without ever suffering from its symptoms. (Hakonarson and Halapi , 2002)
- The genes may never be expressed because of lack of environmental stimuli. Because of the many interactions between genetic predisposition, and the environment, genetic research is very complicated. However, progress is being made and researchers claim to have found certain genes that are one of the causes in asthma in many cases .(Horton et al. 1996**)**
- A study led by researchers Respiratory Cell and Molecular Biology (RCMB) at the University of Southampton has found success in finding a connection between a specific gene and asthma. (Custovic and simpson, 2006)
- This gene is referred to as ADAM33 (a member of the 'a disintegrin and metalloprotease domain' family of proteins.) located on chromosome 20 and is expressed in lung and muscle cells. The ADAM33 gene is believed to be related to asthma as it causes the airways to over-respond and constrict airway passage. (Foley et al., 2007)

Microarray analyses to human are applied to bronchial epithelial cultures to probe for genes regulated by these cytokines and have identified a subset of disease-relevant genes by comparison with cDNA libraries derived from normal and asthmatic bronchial biopsies. Squamous cell carcinoma antigen-1 (SCCA1) and SCCA2, the cysteine and serine protease inhibitors, respectively, showed the highest expression by IL-4 and IL-13, and particularly, SCCA1 was significantly increased in the asthmatic cDNA library. Furthermore, serum levels of SCCA were also elevated in asthmatic patients. Taken together, it was supposed that SCCA may play some role in the pathogenesis of bronchia asthma, and measuring its serum level may be relevant for diagnosing or monitoring the status of bronchial asthma. In a complex disorder such as asthma, this combination of in vitro and in vivo genomic approaches is a powerful discriminatory method enabling identification of novel disease-related genes and their mechanisms of regulation.(Blumenthal and Blumenthal , 2002)

Pathology & pathophysiology of asthma:

Until recently, information on airway pathology in asthma has come largely from post-mortem examination which shows that both large and small airways often contain plugs composed of mucus, serum proteins, inflammatory cells, and cellular debris. Viewed microscopically, airways are infiltrated with eosinophils and mononuclear cells, and there is vasodilation and evidence of microvascular leakage and epithelial disruption The airway smooth muscle is often hypertrophied, which is characterized by new vessel formation, increased numbers of epithelial goblet cells, and deposition of interstitial collagens beneath the epithelium. (Barrios et al., 2006) These features of airway wall remodeling further underscore the importance of chronic, recurrent inflammation in asthma and its effects on the airway. Moreover, these morphologic changes may not be completely reversible.Consequently, research is currently focused on determining whether these changes can be prevented or modified by early diagnosis, avoidance of factors that contribute to asthma severity