Serum Interferon Gamma Induced Protein-10 in Atopic and Non Atopic Infants with Wheezy Chest

Thesis

Submitted for Partial Fulfillment of Master Degree
In Pediatrics

By

Amaal Mohammad El-Hadary
M.B, B.Ch. (2009)

Supervised by

Prof. Elham Mohammad Hossny
Professor of Pediatrics
Faculty of Medicine - Ain Shams University

Dr. Rasha Hassan El-Owaidy
Lecturer of Pediatrics
Faculty of Medicine - Ain shams University

Dr. Neama Lotfy Mohamed
Lecturer of Clinical Pathology
Faculty of Medicine - Ain shams University

Faculty of Medicine
Ain Shams University
2017

Abstract

Introduction: Wheezing is common throughout infancy and childhood except in the neonatal period when it is relatively rare. About 19% of 10-year-old children experience wheezing with an average age of onset of 3 years**.** Bronchiolitis and preschool recurrent wheeze (PSRW) are common pediatric problems causing significant morbidity and mortality in the first years of life. Infants and toddlers with atopy and recurrent wheeze early in life are at greater risk for childhood asthma than non-atopic subjects who wheeze.

Aim of the Work: We sought to investigate serum levels of IP-10 among infants presenting with wheezy chest to anticipate its role in infant wheezes, relation to severity of wheezing illness, presence of signs of respiratory infection or evidence of atopy.

Methodology: This is a cross-sectional controlled study that was carried out in the emergency department and the outpatient clinic of the Children's Hospital, Ain shams university, Cairo, Egypt during the period from December 2014 to March 2015. Informed consent was obtained from parents or care giver of patients before enrolment in the study and the study protocol gained approval from the Ethics' Committee of the Pediatric Department, Ain Shams University.

Results: The study enrolled 90 infants as a stratified non-random sample that is divided into three groups. Each group recruited its sample consecutively. Group A: (n=40): This group included 40 infants who were presented with wheezy chest. Group B (n=25): This group included 25 infants with clinical features suggestive of upper or lower respiratory tract infections (as low grade fever, cough, rhinorrea, conjunctivitis or croup) within 3 days before presentation, and without patient or family history suggestive of allergy. Group C (n=25): This group included 25 healthy infants without history of wheezes and without symptoms of infection or allergic manifestations at time of enrolment. They were enrolled from the outpatient clinic while presenting for nutritional assessment or for circumcision in males.

Conclusion: our data suggest a possible link of serum IP-10 levels to infant wheezes which were not explained exclusively by the association with viral infection. These data might denote a possible future therapeutic role for IP-10 antagonist in severe cases of infant wheezing that are resistant to conventional therapy.

Recommendations: Further wider scale studies are recommended for better elucidation of the IP-10 expression and role in wheezing illness at different age groups.

Investigating various respiratory viral, bacterial, and fungal pathogens in relation to serum IP-10 levels could be worthwhile.

Future studies may be required to investigate the impact of targeting IP-10 in severe cases of pediatric asthma or other wheezing illnesses.

Keywords: Serum Interferon Gamma, Protein-10, Atopic and Non Atopic Infants,h Wheezy Chest

List of Contents

List of Abbreviations

AEC ..... Absolute Eosinophilic Count

ALC..... Absolute Lymphocytic Count

ALSPAC ..... Avon Longitudinal Study of Parents and Children

ANC ..... Absolute Neutrophilic Count

API..... Asthma Predictive Index

BALF..... Bronchial Alveolar Lavage Fluid

BEC ..... Bronchial Epithelial Cell

CBC ..... Complete Blood Count

CCL..... CC Chemokine Ligand

CCL24..... Eotaxin-2

CCL5..... RANTES

CL11..... Eotaxin

CNS..... Central Nervous System

COPD ..... Chronic Obstructive Pulmonary Disease

CoV..... Coronavirus

CRP..... C Reactive Protein

CT..... Computed Topography

CTLs.....cytotoxic T lymphocyte

CXCL ..... CXC Chemokine Ligand

CXCL-9 ..... CXC Ligand 9

CXCL10 ..... IFN-γ-InducibleProtein10

CXCR3..... C-X-C Motif Receptor 3

CXCR4..... C-X-C Motif Receptor 4

CXCR8..... C-X-C Motif Receptor 8

DC..... Dendritic Cell

ECG ..... Electrocardiography

List of Abbreviations

EDTA ..... Ethylene Diamine tetra Acetic Acid

ELISA ..... Enzyme - Linked Immunosorbent Assay

ELR motif..... Amino acid sequence Glu-Leu-Arg

EPW ..... Early-Onset Persistent Wheezers

ETS..... Environmental Tobacco Smoke

ETW..... Early-Onset Transient Wheezers

FGF..... Fibroblast Growth factor

GAGs..... Glycosaminoglycans

GM-CSF ..... Granulocyte - Macrophage Colony-Stimulating Factor

HAART..... Highly Active Anti-retroviral Therapy

HCV ..... Hepatitis C Virus

HDM ..... House Dust Mite

HEV ..... Human EnteroVirus

HIV ..... Human Immunodeficiency Virus

HMPV ..... Human MetapneumoVirus

HSV-2 ..... Herpes Simplex Virus type 2

ICAM..... Intercellular Adhesion Molecule

ICS..... Inhaled Corticosteroids

IFN-γ .....Interferon-γ

IFN-α..... Interferon-α

IFN- β ..... Interferon- β

IgE..... Immunoglobulin E

IL..... Interleukin

IL-2..... Interleukin2

IP-10..... Interferon-γ Inducible Protein of 10 Kilodaltons

List of Abbreviations

IPW ..... Intermediate-Onset Persistent Wheezers

IQR ..... Interquartile Range

I-TAC/CXCL11 ..... Interferon - Inducible T - cell Chemoattractant

iTregs ..... Induced T Regulatory Cell

ITW ..... Intermediate-Onset Transient Wheezers

kB ..... Nuclear Factor Kappa B

LOW ..... Late-Onset Wheezers

LTBI ..... Latent TB Infection

LTRA ..... Leukotriene Receptor Antagonists

LW ..... Late-Onset Wheezers

MDC ..... Myeloid Dendritic Cell

Mig/CXCL9 ..... Interferon - Induced Angiostatic CXC Chemokines, Monokine Induced by Interferon

MS ..... Multiple Sclerosis

NK ..... Natural Killer

nTregs ..... Natural T Regulatory Cell

NW ..... Never Wheezed

OA ..... Osteoarthritis

OD ..... Optical Density

PDAC ..... Pancreatic Ductal Adenocarcinoma

pDC ..... Plasmacytoid Dendritic Cell

PIAMA ..... Prevention and Incidence of Asthma and Mite Allergy

PSCs ..... Pancreatic Stellate Cells

PSRW ..... Preschool Recurrent Wheeze

PW ..... Persistent Wheezers

List of Abbreviations

QF..... QuantiFERON-TB

R..... Spearmnan rank correlation

RA..... Rheumatoid arthritis

RSV..... Respiratory Syncytial Virus

RV..... Rhinovirus

SABA ..... Short-Acting Beta2-Agonists

SARS ..... Severe Acute Respiratory Syndrome

SF ..... Synovial Fluid

SIDRIA..... Italian Studies of Respiratory Disorders in Childhood and the Environment

SLE..... Systemic Lupus Erythromatosis

SPT..... Skin Prick Testing

SS ..... Sjögren Syndrome

SSc ..... Systemic Scleroderma

ST ..... Synovial Tissue

Tc ..... T Cytotoxic

TCRS ..... Tucson Children's Respiratory Study

TEW..... Transient Early Wheezers

TH1 ..... T Helper1

TLR..... Toll-Like Receptor

TNF-α..... Tumour Necrosis Factor-α

Tregs ..... T Regulatory Cell

TSLP..... Thymic Stromal lymphopoietin

URIs..... Upper Respiratory Infections

VEGF ..... Vascular endothelial growth factor

WBC..... White Blood Cells

x2 ..... Kruskal-Wallis Test

List of Tables

List of Tables

List of Figures

Introduction

Wheezing is common throughout infancy and childhood except in the neonatal period when it is relatively rare. About 19% of 10-year-old children experience wheezing with an average age of onset of 3 years ***(Kurukulaaratchy et al., 2002).*** Bronchiolitis and preschool recurrent wheeze (PSRW) are common pediatric problems causing significant morbidity and mortality in the first years of life. Infants and toddlers with atopy and recurrent wheeze early in life are at greater risk for childhood asthma than non-atopic subjects who wheeze ***(Oddy et al., 2002).***

Chemokines are small chemotactic cytokines that modulate inflammatory processes and regulate migration of leucocytes and cell–cell signalling in the immune system. Interferon-ɣ inducible protein of 10 kilodaltons (IP-10), or CXC ligand 10 (CXCL-10), is one of the chemokine (C-X-C motif) receptor 3 (CXCR3) binding chemokines that exerts a stimulating effect on the directional migration of activated and memory Th1 cells and promotes the production of Th1 cytokines ***(Romagnani, 2006).***

Serum IP-10 levels were clearly different in subjects with acute virus-induced asthma compared with those with non–virus-induced asthma and serum IP-10 at presentation

of subjects with acute asthma was strongly associated with more severe airflow obstruction and a reduced b2-agonist bronchodilator response during their initial emergency department presentation ***(Peter et al., 2007).***

Aim of the Work:

We sought to investigate serum levels of IP-10 among infants presenting with wheezy chest to anticipate its role in infant wheezes, relation to severity of wheezing illness, presence of signs of respiratory infection or evidence of atopy.

Infant Wheezing

Wheezing is a common clinical finding in children, especially in the first years of life. Epidemiological studies have shown a high prevalence of wheezing in this age group. Studies in developed countries have shown prevalence between 20% and 30%, with high recurrence of episodes. In developing countries, prevalence rates appear to be higher ***(Ferreira and Wandalsen, 2014).***

Wheezing in infants accounts for a high demand of medical consultations and emergency care services, with relatively high rates of hospitalization. Along with acute respiratory infections, it plays an important role in infant mortality ***(De Jong et al., 2007)***

Definition of infant wheeze:-

Wheeze can be defined as a musical sound, high-pitched and continuous, emitting from the chest during breath exhalation resulting, irrespective of the underlying mechanism, from narrowing of intrathoracic airway and expiratory flow limitation. Although this definition is well known, it may be poorly understood and defined by parents and, therefore, if based only on parental report children may be considered as experiencing wheeze when they, actually, do not. It is important that a health professional

values the wheeze to confirm or reject the diagnosis, always considering that even not all physicians are equally precise in valuing the severity of wheeze ***(Brand et al., 2008).***

Prevalence of infant wheeze:-

Wheezing is common throughout infancy and childhood except in the neonatal period when it is relatively rare. About 19% of 10 years old children experience wheezing with an average age of onset of 3 years ***(Kurukulaaratchy et al., 2003).*** In addition, several population-based birth cohort studies documented that 30% of children suffer from wheezing during respiratory infections before their third birthday. Incidence peaks in those aged 2-8 months. Annual incidence is 11.4% in infants younger than 1 year and 6% in those aged 1-2 years. The illness accounts for 4500 deaths and 90,000 hospital admissions per year. Prevalence may be higher in urban areas ***(Willwerth et al., 2006).*** Recurrent wheezing is common, but most patients outgrow their symptoms by school age. Infant wheezing is sometimes mixed with other causes of noisy breathing including all causes of nasal obstruction in the first 2 years of life. Adenoid hypertrophy is commonly misdiagnosed as bronchospasm on chest auscultation ***(Piippo-Savolainen and Korppi, 2008).***