Transforming Growth Factor beta1 ($TGF–\beta_1$) Profile In Early Childhood Wheezers

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Abstract

Transforming growth factor beta-1 (TGF-β1) may influence asthma by modulating airway inflammation and remodeling. The role of single nucleotide polymorphisms (SNPs) of TGF-β1 in asthma remains inconclusive.

We assessed TGF- β_1 profile in a group of Egyptian infants and young children with recurrent wheezing through measurement of its plasma level and screening for TGF- β_1 promoter polymorphism with special emphasis on the relation of measured parameters to different clinical (age of onset, severity, duration) and laboratory data (IgE-peripheral blood esinophil count). Thirty eight wheezy children aged 8m to 4.75yr (3.3yr±0.98) and a matched control group of thirty five children were recruited for the present study.

Results revealed that the plasma level of TGF-β1 was higher in cases than controls (mean level 3.32 ng/ml ±2.03; p=0.004). Genotype analysis of patients and controls, showed a statistical significant difference in the expression of the homozygous mutant type TT (p=0.043). The correlation of the different genotypes to the serum level of TGF-β1, revealed a statistically significant increase in its level in the homozygous mutant variant TT (p= 0.006) as compared to the wild CC genotype.

In conclusion, children with the TGF-β1- 509 TT genotype were at greater risk of wheezing and asthma, (odds ratio 10.8, 95%CI 0.92-11.6; p=0.04).

Key words: Wheeze- Asthma- TGF-β1- polymorphism

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To The Soul Of My Father..

I dedicate this work.

Contents

List of Abbreviations

ADAM33:	A Disintegrin and Metalloproteiase 33
AHR:	Airway Hyper Reactivity
APC:	Antigen presenting cells
ASM:	Airway smooth muscles
CD:	Cluster differentiation
DCs:	Denderitic cells
DEP:	Diesel Exhaust Particles
DPPIV:	Dipeptidyl peptidase IV
ECM:	Extra cellular matrix
FEV_1:	Forced Expiratory Volume in the first second
GINA:	Global Initiative For Asthma
GPRA:	G protein-coupled receptor for asthma susceptibility
Hgs:	Hepatocyte growth factor-regulated tyrosine kinase substrate
HLA-G:	Human leucocytic antigen
IgE:	Immunoglobulin E
IL:	Interleukin
INF-γ	Interferon gamma
LAP:	Latency-associated peptide
LTBP:	latency TGFβ binding protein
MUC:	Mucin glycoprotein
PHF11:	PHD finger protein 11
RSV:	Respiratory Syncytial Virus
SARA:	Smad anchor for receptor activation
SNP:	Single nucleotide polymorphism
TBRI:	TGF-β receptor I
TBRII:	TGF-β receptor Π
TGF-β1:	Transforming growth factor beta-1
TNF-α:	Tumour necrosis factor alpha
VEGF:	Vascular Endothelial Growth Factor

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Introduction and Aim of work

There is a strong evidence that the prevalence of asthma and wheezing conditions among children has been rising globally; as 25-40% of children experience wheezing in the first five years of life (**Fakhoury, 2008** and **Beasly, 2002**).

The development and expression of asthma may be influenced by a variety of pro- and anti-inflammatory cytokines (**Liebhart et al. 2002**), among them attention has been focused on the role of transforming growth factor beta-1(TGF-β1) in asthma. Transforming growth factor β1 is a pleiotropic cytokine involved in many fibrotic, oncologic and immunologic diseases and is believed to play an essential role in airway inflammation and remodeling processes that occur in asthmatic patients **(Bosse & Rola-Pleszczynski, 2007)**.

Accumulating evidence indicates that TGF-β1 gene may play an important role in airway inflammation (**Fong et al. 2000**) and remodeling (**Kokturk N et al.2003**), suggesting that functional polymorphisms in the TGF-β1 gene that affect its expression may modulate asthma occurrence (**Salam et al. 2007**).

Aim of work

Assessment of TGF-B1 profile in a group of Egyptian infants and young children with recurrent wheezing through measurement of its plasma level and screening for TGF-B1 promoter polymorphism. The relation of measured parameter to different clinical (age of onset, duration, severity) and laboratory data (IgE, peripheral blood eosinophil count) will be assessed as well.

Wheezing in Infants & Young Children

Definition and Epidemiology

A wheeze is a continuous musical sound heard during chest auscultation produced by oscillation of opposing walls of an airway narrowed almost to the point of closure. It can be high-pitched or low-pitched, consist of single or multiple notes, and occur during inspiration or expiration. Wheezes can originate from airways of any size, from the large extra thoracic upper airway to the intra thoracic small airways. In addition to narrowing or compression of the airway, wheezing requires sufficient airflow to generate airway oscillation and produce sound (**Fakhoury, 2008**).

In westernized countries, wheezing affects about one-third of babies in their first year of life (**Landau, 2002**). Also, **Beasly in 2002** reported that early childhood wheezing is extremely common with more than 40% of children experiencing wheezing in the first 5 years of life. However, establishing the real prevalence of wheeze is problematic. Estimations could be affected by a number of factors: doctors' and families' perceptions of "wheeze" may change over time (**Anderson, 1989**); the use of "asthma" as a label for wheezy illness (**Strachan and Anderson 1994**); the influence of public health campaigns (**Magnus & Jaakola 1997**); and a lower threshold

for reporting symptoms that may also be inaccurate (**Britton, 1992**).

Although 20% of all children will have had at least one wheezing illness by one year of age, almost 33% by three years of age, and nearly 50% by six years, less than 15% of children are subsequently diagnosed with asthma based on symptoms of recurrent wheezing, airway obstruction and hyper-responsiveness. Nevertheless, asthma is the most common disease of childhood and confers a significant degree of morbidity, thereby demanding early evaluation and management in the predisposed persistently wheezing infant (**Krawiec et al., 2004**).

Etiology

Wheezing-associated respiratory illnesses in children are often described as asthma. But while most children with asthma wheeze, not all wheezing is related to asthma. Wheezing in infancy and childhood is not a single disorder (**Rusconi et al. 1999**) and is just as likely to be due to causes other than asthma (**Martinez et al. 1995**).

In infants and young children, wheezing is common owing to unique age-specific anatomic and physiologic properties and gender-specific intrinsic lung characteristics (table 1). The etiology of wheezing involves any pathophysiologic process

resulting in impaired airflow, mediated by reduction in airway diameter. This pathophysiologic end point compasses a variety of causes and therefore poses diagnostic difficulties in the evaluation of the young wheezing child younger than five years (table 2) (**Krawiec et al., 2004**).

More than half of the children who wheeze during their first three years have: (**Landau, 2002**).

- congenital or acquired structural abnormalities that reduce the size of the airways;
- cystic fibrosis causing excess production of thick mucus in the airways;
- Bronchiolitis not requiring hospitalization; or viral-induced transient early wheezing.

Understanding the different wheezing disorders may help to identify young children whose wheezing is likely to be related to the development of asthma (**Martinez et al. 1995**) and to avoid inappropriate treatment of children with non-asthma related wheeze (**Lowe et al. 2002**) .

Evaluating wheezing is part of the overall process of diagnosing asthma and other respiratory conditions, and it remains difficult to distinguish young children with atopic asthma from the larger group with wheezing (**Helms & Christie 1999**).

Table (1): Pathophysiologic properties predisposing infants and young children to wheeze (**Krawiec et al., 2004**)

	Effect
Physiologic properties in infants relative to older children/adults	
Reduced bronchial smooth muscle content	↓Structural support ↑Risk of atelectasis
Hyperplasia of bronchial mucous glands	↑Mucous production ↑Risk of obstruction
Reduced radius of conducting airways resulting in overall reduced turbulent flow	↓Conductance ↓Filtration of particles ↑Risk of obstruction ↑↑Risk of atelectasis
Increased resistance in peripheral airways due to decreased airways size	↑Risk of obstruction ↑Work of breathing
Increased Chest wall compliance	↑Work of breathing
Diaphragm Horizontal insertion of the diaphragm to the rib cage Reduced number of fatigue resistant skeletal muscle fibers	↑Risk of atelectasis distal to obstruction
Deficient collateral ventilation	
Gender-based properties related to infantile wheeze	
Females	↓ Lung size
Males	↓ airway conductance (↓Amax FRC)