Sweat Conductivity and Chloride Titration for Diagnosis of Cystic Fibrosis in High Risk Egyptian Children

Thesis
Submitted in partial fulfillment of the degree of M.D in Pediatrics

By
Walaa Aboulkasem Ismail Shahin
M.B, B.Ch, M.Sc
Cairo University

UNDER THE SUPERVISION OF

Prof.
Mona Mostafa El Falaki
Professor of Pediatrics
Cairo University

Prof.
Hala Hamdi Shaaban
Professor of Pediatrics
Cairo University

Prof.
Mona Mohsen Mahmoud
Assistant Professor of Pediatrics
Cairo University

2009
Cairo University

بسم الله الرحمن الرحيم

بناءاً على موافقة الأستاذ الدكتور / نائب رئيس الجامعة بتاريخ ١ / ١٠/ ٢٠٠٩ إجتمعت اللجنة المشكلة من الأساتذة:

أ.د/ منى مصطفى الفلكى	**أستاذ طب الأطفال - كلية الطب - جامعة القاهرة**	**(عن المشرفين)**
أ.د/ ليلى عبد المطلب سليم	**أستاذ طب الأطفال - كلية الطب - جامعة القاهرة**	**(ممتحن داخلى)**
أ.د/ ماجده يحيى الصيفى	**أستاذ طب الأطفال - كلية الطب - جامعة عين شمس**	**(ممتحن خارجى)**

بقاعة الدور السادس - مستشفى الاطفال الجامعى التخصصى لمناقشة علنية لرسالة الدكتوراه فى طب الأطفال

المقدمة من **الطبيبة / ولاء ابو القاسم شاهين**

وذلك فى تمام الساعة (الحادية عشر صباحاً) يوم (الأحد) الموافق ٣١ / ١ / ٢٠١٠

عنوان الرسالة:

" تشخيص مرض التليف الحويصلي في الاطفال المصريين المشكوك باصابتهم بواسطة معايرة الكلوريد وخاصية التوصيل فى العرق "

الملخص:

يعد مرض التليف الحويصلى الرئوى من الامراض الوراثية الاكثر شيوعا فى الاطفال وهو مرض مزمن يصيب عدة أجهزه مما يؤدى إلى إعاقة مرضية مدى الحياة والوفاة المبكرة. نسبة حدوث هذا المرض تختلف تبعاً للاصل العرقى. قليل من التقارير التى تم نشرها عن هذا المرض فى العالم العربى و مصر التى تم فيها عمل دراستين فقط . فى هذه الدراسة قمنا بتقيم نسبة حدوث مرض التليف الحويصلى فى المرضى المصريين الذين يعانون من التهابات مزمنه بالرئه متشابهه مع هذا المرض والمحولين إلى وحده أمراض الصدر والحساسية بمستشفى الاطفال الجامعى جامعة القاهرة بإستخدام طريقة ويسكور (wescor) المعتمدة من اللجنه القومية لمعايير المعامل الاكلينيكية (NCCLS) ومؤسسة التليف الحويصلى (CFF). كما تم عمل تحليل الجينات للحالات الموجبة بهذا الاختبار أوضحت النتائج أن نسبة حدوث هذا المرض فى المرضى الذين تم دراستهم هى ٣٠%. تم تقيم دقة المحلل التوصيلى بإستخدام الحساسية والخصوصية (sensitivity and specificity) وهم ٤٦,٦ % , ١٠٠% على الترتيب. كما أظهر تحليل الجينات أن الطفرة delta F٥٠٨ تمثل ٥٣,٣ % من مرضى التليف الحويصلى بينما فى المجتمعات الامريكية والاوربية تمثل ٧٠% مما يعنى أن المجتمع المصرى له صفات وراثية مختلفة يجب أن تدرس.

وترى اللجنة قبول البحث

DEDICATION

For my Father, Mother, Brothers, my husband
Dr.Yasser Elborai and my kids Hana and Yousef

For all my Professors and Lecturers
For all those who were teaching and backing me
to reach such a stage of education and knowledge

For the patients whom I am asking Allah to cure…

ACKNOWLEDGEMENT

I would like to thank Allah for all his gifts to me and for his support and great help to finish this work.

It is of great honor for me to work with Professor Dr. Mona El-Falaki, professor of Pediatrics, Faculty of medicine, Cairo University. I feel great grattitude and appreciation for her expert guidance, valuable advice and helpful suggestions to deliver this work.

I would like to express my deep appreciation and gratitude to professor Dr. Hala Hamdi Professor of Pediatrics, Faculty of medicine, Cairo University for her close supervision and generous support.

I am deeply thankful to Dr. Mona Mohsen Assistant Professor of Pediatrics, Faculty of medicine, Cairo University for her kind advice and guidance.

Special thanks to Dr. Dina Mehana Lecturer of Clinical and Chemical pathology, Faculty of medicine, Cairo University, for her great help and sincere advice.

Many thanks to Professor Dr. Mohamed Ali Saber Professor of Molecular Biology and Director of Biotechnology and Genetic Engineering unit, Theodore Bilharz Research Institute for his great help in doing the gene analysis.

Lastly, I would like to thank Dr. Hosam Hosny Mahmoud Assistant Professor of Pulmonolgy, Faculty of medicine, Cairo University for his assistance in referring the patients to our unit and doing the bronchoscope for selected ones.

ABSTRACT

Cystic fibrosis (CF) is the most common autosomal recessive disorder among Caucasians. Early diagnosis and advances in the care of patients with CF have improved survival. Limited data is available regarding its prevalence in high risk Egyptians. It was generally believed that CF is rare among Arabs; however, the few studies available are suspecting the presence of many undiagnosed patients. The aim of the present study is to determine the prevalence of CF in high risk Egyptian patients referred to the allergy and pulmonology unit through a period of one year. Since the sweat chloride test remains the gold standard for the diagnosis of CF, we used it in the diagnosis of our cases using the standardized methods which is approved by the NCCLS (National Committee for Clinical Laboratory Standards) and the CFF (cystic fibrosis foundation) guidelines which are pilocarpine iontophoresis for induction of sweat and macroduct collector for sweat collection. Analysis of the samples was done by the conductivity analyzer and by the chloridometer. Gene analysis of the positive cases was performed using gene amplification by PCR followed DNA sequencing for detection of delta F508 mutation. Results of the present study showed that the prevalence of CF in high risk patients is 30%, which is more than expected for our population from previous studies. Delta F508 represents 53.3% of the CF patients. The accuracy of the conductivity analyzer was assessed by sensitivity and specificity which are 46% and 100% respectively. By correlation of the severity of the diseases with the sweat test values; it was statistically insignificant. In conclusion, further studies are required for accurate assessment of the CF prevalence and the identification of different mutations in the Egyptian population.

Key words: Cystic Fibrosis/ Sweat chloride test/ Delta F508/ Egypt

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SUMMARY IN ARABIC

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List of abbreviations

AAV	Adeno-Associated Virus
ABPA	allergic bronchopulmonary aspergillosis
ACC	N-AcetylCysteine
ACTs	Airway-Clearance Therapies
AGH	Abnormal Glucose Homeostasis
ATP	Adenosine Tri-Phosphate
BMR	Basal Metabolic Rate
cAMP	Cyclic Adenosine Mono-Phosphate
CF	Cystic fibrosis
CFAA	Cystic fibrosis associated arthritis
CFRD	Cystic fibrosis-related diabetes
CFTR	Cystic fibrosis transmembrane conductance regulator
ChT	Chemotrypsin
CLSI	Clinical and Laboratory Standards Institute
COPD	Chronic Obstructive Pulmonary Disease
CPX	8-CycloPentyl-1, 3-dipropylXanthine
CT	Computed Tomography
DHLA	DiHydroLipoic Acid
DM1	type 1 Diabetes Mellitus
DM2	type 2 Diabetes Mellitus
E1	elastase-1
ENaC	Epithelial Na^+ Channel
FEF	Forced Expiratory Flow rate
FEV1	Forced Expiratory Volume in 1 sec
FRC_{pleth}	Functional Residual Capacity made by plethysmography
FVC	Forced Vital Capacity
GER	GastroEsophageal Reflux
GSH	Reduced Glutathione
GSSG	Oxidized Glutathione
HPOA	Hypertrophic Pulmonary OsteoArthropathy
HRCT	High Resolution Computed Tomography
ICS	Inhaled Corticosteroids
IL	Interleukin
IRT	Immunoreactive Trypsinogen
IVIG	IntraVenous ImmunoGlobulin
mA	milli ampere
MSDs	Membrane-Spanning Domains
NAC	N-Acetyl L-cysteine
NAL	N-AcysteLyn
NBD	Nucleotide-Binding Domains

NCCLS	National Committee for Clinical Laboratory Standards
NPD	Nasal Potential Difference
NPV	Negative Predictive Value
NSAID	Non Steroidal Anti Inflammatory Drug
OGTT	Oral Glucose Tolerance Test
PCD	Primary Ciliary Dyskinesia
PCR	Polymerase Chain Reaction
PD	Potential Difference
PI	Pancreatic Insufficiency
PPV	Positive Predictive Value
PS	Pancreatic Sufficiency
RD	Regulatory Domain
Rh Trx	Recombinant Human Thioredoxin
RV	Residual Volume
SBDS	Shwachman-Bodian-Diamond Syndrome
SD	Standard Deviation
SLPI	Secretory LeukoProtease Inhibitor
SPT	Secretin-Pancreozymin Test
TNF	Tumor Necrosis Factor

REVIEW OF LITERATURE

INTRODUCTION AND AIM OF THE WORK

Cystic fibrosis is the most common potentially lethal genetic disease among populations of white Caucasian descent, such as those of Europe, North America and Australasia, being caused by mutations of the cystic fibrosis transmembrane conductance regulator (CFTR gene) ***(Kraemer, et al, 2006).***

Cystic fibrosis is a multisystem disorder affecting many organs including the lungs, gastrointestinal tract, pancreas and liver. Failure to thrive is a common presentation of undiagnosed children with CF; and poor nutrition may be a problem in the children and adults diagnosed with CF which may worsen as the disease progresses ***(Smyth & Walters, 2007).***

The lung affection is characterized by dehydration of airway surface liquid and impaired mucociliary clearance. As a result, there is difficulty clearing pathogens from the lung, and patients experience chronic pulmonary infections and inflammation. Although cystic fibrosis is a complex disorder affecting many organs, 85% of the mortality is a result of lung disease ***(Flume, et al, 2009).***

The median age at death is approximately 25 years. Every year, many children with cystic fibrosis die from respiratory failure ***(Liou, et al, 2008).***

Cystic fibrosis incidence varies according to ethnic group, ranging from one in 2,000 to one in 3,500 Caucasians born in Europe, the United States, and Canada, and with the lowest incidence among hispanics (1:8400 birth), African-Americans (1:15000 births), and the Asian population of Hawaii (1:89000 births) ***(Rodrigues, et al, 2008).***

For a long time, cystic fibrosis was thought to be a rarity in the Arab world (northern African countries bordering the Mediterranean and Middle East). Recently, case reports from several Arabic countries have been published including Saudi Arabia, Bahrain, Tunisia, Algeria and Lebanon. It was found that the incidence of CF in the Middle East varies according to the ethnic background and the degree of consanguinity. Consanguinity is claimed to be about 65 % in the Arab world. Estimates range from 1 in 2,560 to 1 in 15,876 ***(Kambouris, et al, 2000).***

Limited data is available regarding cystic fibrosis prevalence in high risk Egyptians. Cystic fibrosis has been believed to occur infrequently in Egypt; only few papers suggested its presence. In a study done by Abdel Salam and her colleagues aiming at evaluating the magnitude of the CF problem in Egypt, the prevalence rate was reported to be 1:2664 in 18560 screened newborns and 1:56 in a series of 224 high risk children ***(AbdelSalam, et al, 1993)*.**

The great variability in the incidence of Cystic Fibrosis is not only influenced by the ethnic makeup but also by rate of consanguinity, geographical origin, certain tribal descent and religious background prevalent in a certain population. Therefore, CF incidence and specific mutations have to be assessed specifically for any population ***(Kambouris, et al, 2000).***

The criteria for the diagnosis of CF include: the presence of one or more characteristic phenotypic features or a history of CF in a sibling or a positive newborn screening test result, and increased sweat chloride concentration by pilocarpine iontophoresis on two or more occasions, or identification of two CF mutations or demonstration of abnormal nasal epithelial ion transport. The quantitative pilocarpine iontophoresis sweat test