TRACE ELEMENTS IN CONGENITAL CYANOTIC HEART DISEASE

THESIS

Submitted for Partial Fulfillment of
The Master Degree in the Pediatrics
By

Ghassan Isa Salama Al Awawda

SUPERVISED BY

Prof.Dr.Mohammad Ali Hegazi

Assistant Professor of Pediatrics
Faculty of Medicine
Cairo University

Prof.Dr.Mona.M.H.Mahmoud

Assistant Professor of Pediatrics
Faculty of Medicine
Cairo University

Prof.Dr.Mohammad Shahata Abdullah

Assistant Professor of Chemical & Clinical Pathology

Faculty of Medicine
Cairo University

Faculty of Medicine

CAIRO UNIVERSITY

٢٠٠٩

Abstract .

The Trace Elements in Congenital Cyanotic Heart Disease

Background: The trace elements are essential micronutrients that have important physiological, metabolic, and homeostatic roles in the human being. Up till now the actually role and effect of the trace elements on myocardial metabolism specifically on congenital cyanotic heart disease is not entirely clear.

Objective: This study aimed to detect the serum level of selected trace elements (zinc, copper and selenium), and evaluate its effect and relation in congenital cyanotic heart disease.

Methodology: This study had enrolled upon 50 children, included 30 patients with congenital cyanotic heart disease and 20 age matched normal healthy children as control group. All groups were subjected to thorough clinical history, examination and specific cardiac investigation as well as detection of serum levels of zinc, copper and selenium. All results were statistical analyzed.

Results: The current study revealed that a highly significant decrease in the serum level of both zinc and selenium ($p<0.001$ and $p<0.\ 01$), however serum copper level has non significant increase in congenial cyanotic heart disease, were ($p>0.05$). There was non significant correlation between the mean serum levels of trace elements and the hemodynamic parameters,. Also there were non significant correlations between the age and sex of the studied group and the mean serum levels of these trace elements ($p>0.05$).

Conclusion: Congenital cyanotic heart disease were associated with a highly significant decrease in the mean serum selenium and zinc levels, when compared with control group and non significant increase the mean serum copper levels.

Changes in these trace elements suggested to play an important role in the pathogenesis of myocardial damage in congenital cyanotic heart disease.
.

Key words: Zinc, Copper, Selenium and congenital cyanotic heart disease.

ACKNOWLEDGEMENT

First of all, great thanks for ALLAH, for helping me in my life and in this work.

I would like to express my deepest gratitude to my great Prof. Mohammed Ali Hegazi ,Professor of Pediatrics, Faculty of Medicine - Cairo University for her creative advices, continuous encouragement, unlimited help, continuous guidance and support throughout this work.

I would like to express my deep thank and gratitude to Prof. **Mona.M.H.Mahmoud** *, Assistant Professor of Pediatrics, Faculty of Medicine - Cairo University.*

I do also thank Prof. Mohammed Shehata Abdullah , Assistant Professor of Chemical & Clinical pathology , Faculty of Medicine - Cairo University.

Finely, I would like to thank all the staff members in Pediatric Department, and patients and their parents in our study.

I would like to dedicate my assay to my very precious people who are support me hardly to complete my postgraduate education. .

CONTENTS

List of tables

List of figures

Lest of the abbreviations

AI: Adequate Intake.

ASD: Atrial septal defect.

CCHD: Congenital Cyanotic Heart Disease.

DORV: Double Outlet Right Ventricle.

FIAM: Free Ion Activity Model.

GPx: Glutathione Peroxides.

HLHS: Hypoplastic Left Heart Syndrome.

PA: Pulmonary Atreasia.

RDAs. : Recommended Dietary Allowances

RNIs: Recommended nutrition Intakes.

ROS: Reactive Oxygen Species.

Se: Selenium.

SIDS: Sudden Infant Death Syndrome.

SOD: Superoxide Dismutase.

TAPVR: Total Anomalies Pulmonary Venus Return.

TGA: Transposition of Great Arteries.

TOF: Teatrology of Fallot.

VPS: Valve Pulmonary stenosis.

VSD: Ventricular Septal Defect.

INTRODUCTION

Congenital heart disease (CHD) represent 3-4% of all cardiac defects, **(Ference C et al., 1997).** In cyanotic congenital heart disease, oxygen delivery is impaired either by reduced pulmonary perfusion or by limited entry of oxygenated blood into the systemic circulation leading to hypoxemia **(Trittenwein et al., 1997)** . Were hypoxia alters every aspect of cellular physiology.

Trace elements are being increasingly recognized as essential mediators of the development and progression of heart diseases.

It is well known that Se, Zn, and Cu in serum can affect certain heart diseases such as Keshan disease, heart failure, cardiomyopathy, and atherosclerosis (**Topuzglu G. et al., 2003**). Therefore, trace elements may play an important role in the pathogenesis and severity of the heart diseases.

Selenium is a part of glutathione peroxides in the cytosol and mitochondria, which protects biomembranes against destruction.

Selenium is also a central enzyme for eliminating oxygen free radicals and peroxides. Enzymes such as superoxide dismutase and glutathione peroxides contain either copper and zinc or manganese. Therefore, trace elements like Se, Zn and Cu have an antioxidant role in many essential enzyme systems (**Prasad AS. et al., 2004**). In the lack of superoxide dismutase, superoxide anions react with hydrogen peroxide to form hydroxide radicals, and cause lipid peroxides and destruction of the cell membranes. On theoretical grounds, trace elements may be protective against oxygen free radicals in the development of cardiovascular disease (**Marin J. et al., 1995)**.

Aim Of The Work

The aim of the present study was to evaluate the status of selenium, zinc, and copper in patients with cyanotic congenital heart disease. To investigate potential relation between serum trace elements concentrations and the clinical and hemodynamic.

CONGENITAL HEART DISEASEIS

Definition and Etiology

Cardiac malformations represent at birth are an important component of pediatric cardiovascular disease and constitute a major percentage of clinically significant birth defects, with an estimated prevalence of 4 to 5 per 1000 live births, ventricular septal defect (VSD), Tetrology of Fallot (TOF), and transposition of great arteries (D-TGA), were represented the most common congenital heart disease (CHD) **(Roguin N. et al., 1995).** VSD has been reported to be the most frequent cardiac defect in various studies of live births and stillbirth **(Hyett J. et al., 1997).** While TOF is the most common cyanotic CHD, affecting 2.5/10.000 live births **(Ferencz C. et al., 1985).** It represents 4%-7.5 of all forms of cardiac malformations.**(Boughman, J.A et al., 1987).**

The exact etiology of CHD is still unknown, However, resent advances in molecular genetics demonstrates that CHD is a multifactorial inheritance disorders that results from complex interactions between genetic susceptibility , adverse maternal conditions and teratogenic influences as advanced maternal age, maternal diabetes mellitus, viral infections e.g. rubella, CMV, herpes zoster, mumps, measles, exposure to radiations or drugs abuse, e.g., alcohol ,progestin, anticonvulsants, thalidomide, warfarin and insecticides.

.

Risk Factors Found In Congenital Heart Disease and Chromosomal Aneuploid

The risk factors for fetuses with congenital heart disease may be grouped into two main categories, fetal factors and maternal factors. Fetal factors include: chromosomal abnormalities, extracardiac anatomic abnormalities, nonimmune hydrops fetalis, fetal cardiac arrhythmia, or suspected cardiac anomaly on routine ultrasound. The maternal factors include: family history of congenital heart disease, maternal metabolic disorders, or maternal teratogen exposure.

The association of genetic predisposition to cardiac defects is receiving more attention as a result of fetal echocardiographic early diagnosis, surgical interventions and advances, and greater sophistication of cytogenetic and molecular genetic techniques. As with all birth defects, chromosomal aneuploidy should be suspected in any newborn with congenital heart disease. The association of heart disease with a specific pattern dysmorphic features may suggest a syndrome. Maternal history will identify those associated with the known teratogens. Clinical examination will identify those liable to be associated with a chromosomal deletion not apparent to routine karyotype analysis. A combination of family history and dysmorphic features can identify a further group of heart defects associated with monogenic syndromes. In a small proportion of isolated heart defects, the pedigree is sufficient to recognize monogenic inheritance **(Lammer,.et al., 1985).**

Embryogenesis of the Cardiovascular System and the Development of Cardiac Anomalies

The primitive heart begins as a pair of endocardial heart tubes that develop before the end of the third week and begin to fuse together to form the primitive cardiovascular system. The heart has four primary developing areas: an inlet or atrium, a central dilatation or ventricle, the bulbous cordis leading to the single outlet artery - the truncus arteriosus. The heart is functional by the end of the fifth week of fetal development as it is converted from a simple primary tube to a four-chamber, valved organ. The cardiovascular system is the first organ to reach a functional state in the embryo **(Callen, et al,.1994).**

Aneuploidy

A cardiovascularneuploidy is an abnormality of the chromosomes that implies "not a good set". Any deviation from the diploid number of 46 chromosomes is called aneurploidy. The cells may be hypodiploid (usually 45) or hyperdiploid (usually 47 to 49). Cytogeneticists tend to apply the term to numerical departures from the norm: monosomies, trisomies, and tetrasomies. The incidence of chromosomal abnormalities is still significantly increased (15%-30%), and thus appropriate genetic counseling is warranted. **(Abuhamad. 1997**).

Prevention

Prevention of congenital cardiovascular defects has been hampered by a lack of information about modifiable risk factors for abnormalities in cardiac development. Over the past decade, there have been major breakthroughs in the understanding of inherited causes of congenital heart disease, including the identification of specific genetic abnormalities for some types of malformations.

Although relatively less information has been available on non inherited modifiable factors that may have an adverse effect on the fetal heart, there is a growing body of epidemiological literature on this topic. This statement summarizes the currently available literature on potential fetal exposures that might alter risk for cardiovascular defects.

Information is summarized for periconceptional multivitamin or folic acid intake, which may reduce the risk of cardiac disease in the fetus, and for additional types of potential exposures that may increase the risk, including maternal illnesses, maternal therapeutic and nontherapeutic drug exposures, environmental exposures, and paternal exposures. Information is highlighted regarding definitive risk factors such as maternal rubella; phenylketonuria; pregestational diabetes; exposure to thalidomide, vitamin A and indomethacin tocolysis **(Kathy J.et al., 2007).**

Relative Frequency of Major Congenital Heart Lesions

TABLE (1) Relative Frequency of Major Congenital Heart Lesions :

LESION	**% OF ALL LESIONS**
Ventricular septal defect	**35–30**
Atrial septal defect (secundum)	**6–8**
Patent ductus arteriosus	**6–8**
Coarctation of aorta	**5–7**
Tetralogy of Fallot	**5–7**
Pulmonary valve stenosis	**5–7**
Aortic valve stenosis	**4–7**
d-Transposition of great arteries	**3–5**
Hypoplastic left ventricle	**1–3**
Truncus arteriosus	**1–2**
Total anomalous pulmonary venous return	**1–2**
Tricuspid atresia	**1–2**
Single ventricle	**1–2**
Double-outlet right ventricle	**1–2**
Others	**5–10**

Michael D Freed. 2001) has classified congenital heart diseases into deferent groups.

Classification of Congenital Heart Disease:

I. Intracardiac Communication between the systemic and pulmonary circulation , usually without cyanosis:

- Ventricular septal defect.
- Atrial septal defect.
- Partial anomalous pulmonary venous connection.
- Common atrioventricular canal defect.

II. Extracardiac communication between the systemic and pulmonary circulations, usually without cyanosis.

- Patent ductus arteriosus.
- Sinus of valsalva fistula.

III. Valvular and vascular malformations of the left side of the heart with right to left bi-directional, or no shunt:

- Coarcotation of the aorta.
- Valvular aortic stenosis.
- Suprevalvular aortic stenosis.
- Subvalvular aortic stenosis.
- Bicuspid aortic valve.
- Congenital mitral regurgitation.