Medical studies department

Relation of Vascular Endothelial Growth Factor and Insulin Like Growth factor-1 to the Development of Retinopathy in Premature Infants

Thesis

Submitted for Fulfillment of Ph.D. in Childhood Studies
(Child Health and Nutrition)
Medical Studies Department

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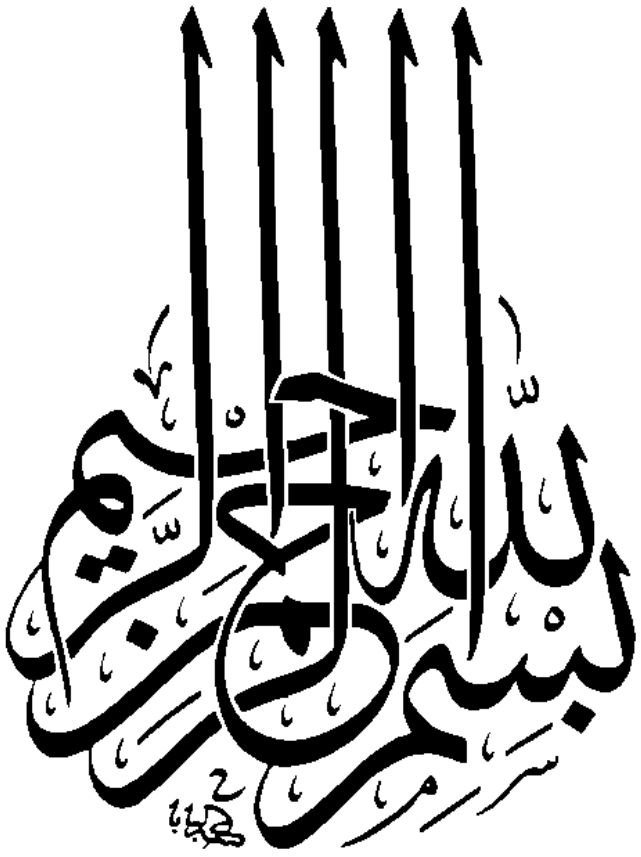
2010


بسم الله الرحمن الرحيم

ACKNOWLEDGEMENT

I wish to express my deepest gratitude to Prof. Dr. Rehab Abd El- Kader Mahmoud, Professor of Pediatrics, Institute of Post Graduate childhood Studies, Ain Shams University for her continuous encouragement, patience and help throughout the study.

Grateful acknowledgement to Prof. Dr. Inas Raafat Abdel Hamid, Professor of Child Health, Department of Child Health, National research Center for her continuous support and help.

Special thanks, appreciation and respect to Dr. Ihab Saad Othman, Associate Professor of Ophthalmology, Cairo University, for his patience and support. Dr. Ihab Saad Othman carried out all the ocular examination throughout the study with a lot of interest and care.

I would like to thank Prof. Dr. Azza Gabre, Professor of Child Health, Department of Child Health, National Research Center, for her great help.

I am grateful to Prof. Dr. Gloria Gameel Sidhom, Professor of Clinical Pathology, National Research Center, for her helpful advises and support. Prof. Dr. Gloria carried out the entire laboratory works included in the thesis.

I would also like to express my thanks to all staff members of Almaza Charity Neonatal Unit, for providing all the cases in the study.

I am also grateful to the babies included in the study and their families.

Finally, I must thank my family for their support, encouragement and help.

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LIST OF ABBREVIATIONS

AGA : Appropriate gestational age
ALS : Acid labile subunit
AAP : American academy of pediatrics
AP-ROP : Aggressive posterior retinopathy of prematurity
bFGF : Basic fibroblast growth factor
BP : Blood pressure
BPD : Broncho pulmonary dysplasia
BUN : Blood urea nitrogen
BW : Birth weight
CBC : Complete blood count
ChBF : Chroidal blood flow
CO_2 : Carbon Dioxide
CRP : C-reactive protein
Cryo ROP : Cryotherapy for retinopathy of prematurity
CSF : Cerebrospinal fluid
DOB : Date of birth
EEG : Electroencephalogram
EGF : Epidermal growth factor
ELBW : Extreme low birth weight
ESR : Erythrocyte sedimentation rate
ETROP : Early treatment retinopathy of prematurity
FDP : Fibrin degradation products
FGF : Fibroplast growth factor
FiO_2 : Flow of inspired oxygen
Flt-1 : Fms-related tyrosine kinase-1
GA : Gestational age
GH : Growth hormone
GHD : Growth hormone deficiency
HC : Head circumference
HR : Heart rate
hGH : Human growth hormone
IGF : Insulin like growth factor

IGFBP : Insulin like growth factor binding protein
IOP : Intraocular pressure
IRBP : Interstitial retinal binding protein
IUGR : Intra uterine growth retardation
IVH : Intraventricular hemorrhage
kDa : Kilodaltons
KDR : Kinase insert domain receptor
LBW : Low birth weight
LOC : Level of consciousness
MSA : Multiplication stimulating factor
MW : Molecular weight
NBS : New Ballard Score
NCPAP : Nasal continuous positive airway pressure
ng : Nanogram
NICU : Neonatal intensive care unit
NJ : Neonatal jaundice
NS : Neonatal sepsis
NSILA : Non suppressible insulin like activity
$PaCO_2$: Partial arterial CO_2 tension
PaO_2 : Partial arterial oxygen tension
PDA : Patent ductus arteriosis
PDGF : Platelet derived growth factor
pg : Picogram
PGE_2 : Prostaglandin E_2
PN : Post natal
PT : Prothrombin time
PTT : Partial thromboplastin time
PUFAS : Poly unsaturated fatty acid
RBF : Retinal blood flow
RDS : Respiratory distress syndrome
RLF :Retrolental fibroplasias
ROP : Retinopathy of prematurity
RPE : Retinal pigment epithelium
RR : Respiratory rate

SD : Standard deviation
SGA : Small gestational age
SGOT : Serum glutamate oxaloacetate transaminase
SGPT : Serum glutamate pyruvate transaminase
Sm : Somatomedins
SpO_2 : Oxygen saturation level
STOP-ROP : Supplemental theraputic oxygen for prethreshold Retinopathy of prematurity
TGF : Tumor growth factor
TGF-B : Tumor growth factor-beta
TNF : Tumor necrosis factor
VEGF : Vascular endothelial growth factor
VEGFR : Vascular endothelial growth factor receptor
VLBW : Very low birth weight
VPF : Vascular permeability factor
Wt : Weight
Wt at exam : Weight at examination

ABSTRACT

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Relation of Vascular Endothelial Growth Factor and Insulin Like Growth Factor-1 to the Development of Retinopathy in Premature Infants

Background: Survival of premature infants in Egypt has been increased in the past few years due to advances in antenatal and neonatal care. This has resulted in a population of infants at high risk of developing retinopathy of prematurity (ROP).

Objective: To evaluate the role of cytokines (Insulin Like Growth Factor-1 "IGF-1" and Vascular Endothelial Growth Factor "VEGF") in serum of premature infants as possible diagnostic markers for ROP and to assess the risk factors for the occurrence and severity of ROP such as birth weight, gestational age, oxygen therapy …etc.

Methods: Eighty three premature neonates who were admitted to the neonatal intensive care unit (NICU) of Almaza charity neonatal care unit in Cairo were included in this study. They were classified into two groups: those developing ROP (n = 34) and those without ROP (n=49). The ROP group was subdivided to: mild cases (those with stages I and II ROP) and severe cases (those with stages III and V ROP). All babies were examined during their stay in the NICU by the attending staff and also ophthalmic examination was performed during incubation to detect ROP. We obtained serum from each infant at 4 to 6 weeks postnatal age for estimation of IGF-1 and VEGF levels.

Results: Analysis of various risk factors for development of ROP showed that small gestational age (GA), low birth weight, prolonged incubation duration, oxygen therapy, respiratory distress syndrome (RDS) and neonatal jaundice were significant risk factors for ROP, while regarding severity of ROP, neonates having respiratory distress syndrome and those with small head circumference were found to be at higher risk of developing severe ROP. Univariate statistical analysis revealed that low IGF-1 and high VEGF serum levels can be useful as indicators in ROP screening but as regards severity they were not predictive markers.

Conclusions: IGF-1 and VEGF serum levels in premature infants could be useful indicators in ROP screening. Elevated VEGF serum level helps to predict the probability of suffering from the illness.

Key words: IGF-1, VEGF, retinopathy of prematurity, risk factors.

INTRODUCTION

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Retinopathy of prematurity has been identified in 1984 by the Cryo-ROP cooperative group, as a retinal vasoproliferative condition that evolves into five stages. Alongside these stages, other destructive changes also occur inside the eye. The destructive activity is known as "plus disease". The signs of plus disease include: engorgement and tortuosity of the posterior pole retinal vessels, iris vessels engorgement, pupil rigidity and vitreous haze ***(Cryo-ROP, 2001).***

The blood vessels in the retina of premature and/or low birth weight infants are immature and underdeveloped. Following delivery, the blood vessels continue to grow and spread throughout the retina. These abnormal blood vessels are fragile and can leak scarring the retina and pulling it out of position leading to retinal detachment (***Stout and Stout, 2003)***. Retinopathy of prematurity is an important cause of childhood blindness worldwide ***(Brian and Neil, 2009).***

Various risk factors to which the neonates are exposed, i.e. oxygen therapy, apnea, anemia, etc… may aggravate the insult to which the under developed or premature eye is exposed to ***(Kim et al., 2004).***

It has been proposed that vasculogenesis is the result of complex interactions between growth factors (cytokines like IGF-1 and VEGF) produced both locally and systemically which stimulate or inhibit differentiation, proliferation, migration, and maturation of endothelial cells. This process is incriminated in the development of ROP ***(Villegas et al., 2006).***

IGF-I is critical to normal retinal vascular development, and its deficiency is associated with the lack of vascular growth that sets the stage for subsequent hypoxia-driven proliferative ROP. In addition, linking IGF-I and VEGF, it was found that IGF-I receptor activation controls maximum VEGF activation of the endothelial cell survival pathway. Low IGF-I might be used to predict later development of ROP (***Lofqvist et al., 2006***).

Findings indicate that VEGF, in addition to its function as an angiogenesis factor, may also act as a survival factor for newly formed capillaries in the developing retina and suggest an important role for VEGF in the pathogenesis of human ROP **(*Smith, 2008*).**

Aim of The Study:

1. We aimed to evaluate the role of cytokine levels (IGF-1 and VEGF) in serum of premature infants as possible diagnostic markers for ROP.
2. We also aimed to analyze other factors which may act as risk factors for occurrence and severity of ROP like birth weight and gestational age.