

**Serum Epidermal Growth Factor Receptor
Level In Children With Brain Tumors**

Thesis submitted in partial fulfillment for master degree in

Pediatrics

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا بِمَا

عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ

الْحَكِيمُ

مِصْبَاحُ اللَّهِ الْعَظِيمِ

سُورَةُ الْبَقَرَةِ آيَةُ (٣٢)

Dedication

To:

Soul of my parents

To::

My Brother and sisters

To:

My sincere wife

To:

*My lovely children
Raghad, Mohamed and Ahmed*

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List of Abbreviations

<i>ADCC</i>	Antibody-dependent cellular cytotoxicity
<i>AFP</i>	Alpha-fetoprotein
<i>ALL</i>	Acute Lymphoblastic Leukaemia
<i>ATP</i>	Adenosine triphosphate
<i>CBT</i>	Childhood Brain Tumors
<i>CCG</i>	Children's Cancer Study Group
<i>cGy</i>	centi-Gray
<i>CNS</i>	Central nervous system
<i>CR 1</i>	Cysteine-Rich 1
<i>CRT</i>	Cranial radiation therapy
<i>CSF</i>	Cerebro-spinal fluid
<i>CT</i>	Computed tomography
<i>Cys</i>	Cysteine
<i>3D-CRT</i>	Three-Dimensional Conformal Radiotherapy
<i>DNA</i>	Deoxyribo Nucleic Acid
<i>EGF</i>	Epidermal growth factor
<i>EGFR</i>	Epidermal Growth Factor Receptor
<i>EGFR vIII</i>	Epidermal Growth Factor Receptor variant three
<i>ELISA</i>	Enzyme linked immuno-sorbant assay
<i>ErbB</i>	Epidermal receptor binding-B
<i>ERK</i>	Epidermal receptor kinase
<i>FDG</i>	F-deoxyglucose
<i>Fmol/ml</i>	Femto mole per milliliter
<i>GFR</i>	Glomerular filtration rate
<i>GH</i>	Growth hormone
<i>GnRH</i>	Gonadotropin releasing hormone
<i>HB-EGF</i>	Heparin-binding epidermal growth factor-like growth factor
<i>hCG</i>	Human chorionic gondadotropin
<i>Her-2</i>	Human epidermal growth factor receptor-2
<i>ICP</i>	Intracranial pressure
<i>ICT</i>	Intracranial tension
<i>IgG</i>	Immunoglobulin G

<i>INR</i>	International normalized ratio
<i>I Q</i>	Intelligence quotient
<i>KDa</i>	Kilo-dalton
<i>LEU</i>	Leucine
<i>MAbs</i>	Monoclonal antibodies
<i>MAPK</i>	Mitogen activated protein kinase
<i>MRA</i>	Magnetic resonance angiography
<i>MRI</i>	Magnetic resonance imaging
<i>mRNA</i>	Messenger Ribo Nucleic Acid
<i>N</i>	Number
<i>NF-1</i>	Neurofibromatosis type 1
<i>NOC</i>	N-nitroso compounds
<i>NS</i>	No significance
<i>NSCLC</i>	Non-small cell lung cancer
<i>NSS</i>	Neurological severity scale
<i>OSR</i>	Overall survival rate
<i>PET</i>	Positron emission tomography
<i>PI3K</i>	Phosphatidyl inositol-3 kinase
<i>PKC</i>	Protein kinase c
<i>PNET</i>	Primitive neuroectodermal tumor
<i>PNET-MB</i>	Primitive neuroectodermal tumor- Medulloblastoma
<i>P value</i>	Probability value
<i>RAS</i>	Receptor activation signal
<i>ROC_s</i>	Receiver operating characteristics curve
<i>RTK</i>	Receptor tyrosine kinase
<i>SD</i>	Standard deviation
<i>Sig</i>	Significance
<i>Src</i>	Signaling receptor-C
<i>TGF-α</i>	Transforming growth factor- α
<i>TK</i>	Tyrosine kinase
<i>TMB</i>	Tetra-methyl benzidine
<i>WHO</i>	World Heath Organization

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Introduction

Brain tumors are a heterogeneous group of diseases that collectively are the second most frequent malignancy in childhood and adolescence. Mortality among this group approaches 45%. In addition, these patients have the highest morbidity, primarily neurologic, of all childhood malignancies. However, outcomes have improved over time with innovations in neurosurgery and radiation therapy as well as identification of chemotherapy as a therapeutic modality (*Kuttesch et al., 2008*).

Epidermal Growth Factor Receptor (EGFR) is a transmembrane cell surface receptor that plays an important and complex role in a wide variety of pathophysiological disorders including cancer. EGFR is a member of tyrosine kinases. The ligand-binding component of EGFR resides on the exterior surface of the cell and can be activated by hormones, growth factors, neurotransmitters and other cellular regulators (*Mendelson and Baselga, 2000*).

When EGFR is activated by epidermal growth factor and other ligands, a variety of complex intracellular signaling pathways are triggered resulting in regulation of diverse cellular processes such as cell division, cell survival and cell motility (*Yarden and Slwkowsky, 2001*).

Normally, EGFR activation is regulated. But when such regulation is disrupted, ongoing stimulation of cell replication results. This deregulation predisposes to the development and maintenance of cancer by initiating a continued uncontrolled cell proliferation. Deregulation may result from EGFR gene amplification that results in more growth factor receptors on the cell surface, increased EGFR transcription or translation that results in overexpression of cell surface growth factor receptors and increased EGFR- mediated signaling (*Brugge and McCormick, 1999*).

Based on structure and function of EGFR, two antireceptor therapeutic strategies have been developed. The first strategy uses humanized monoclonal antibodies that block ligand binding to the extracellular domain. The second approach uses small-molecule inhibitors to inhibit the EGFR tyrosine kinase, which is on the cytoplasmic side of the receptor. A number of EGFR inhibitors have been developed that can arrest tumor growth and, in some cases, cause tumor regression. When used in combination with cytotoxic treatments, chemotherapy or radiation, EGFR inhibitors have been able to potentiate their anticancer activity (*Ritter and Arteaga, 2003*).

Aim of the Work

The aim of this study is to assess serum epidermal growth factor receptor levels in children with brain tumors and to relate its level to different clinicopathological features of the patients

Brain Tumors

Tumors in childhood represent the second most common cause of death after accidents and malignant brain tumors are the first cause of cancer death among children. These tumors account for about 16% of all childhood malignancy being second only to leukemia (*Baldwin and Preston-Martin, 2004*).

Incidence:

The incidence of childhood CNS tumors appeared to be on the rise. This higher incidence was likely due to the increased use of magnetic resonance imaging (MRI) to evaluate children with neurologic conditions and to an increase in microscopical confirmation techniques rather than true increase in the disease frequency (*Pizzo et al., 2006*).

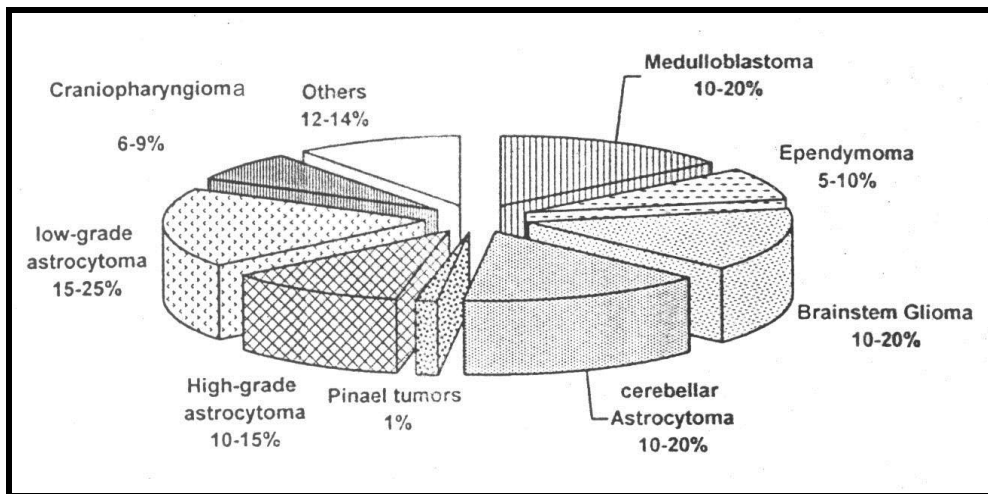


Fig. (1): Incidence of the common pediatric CNS tumors (*Pizzo et al., 2006*).