Correlation of Serum Level of Metalloproteinase-9 in Newborns with Hypoxic Ischemic Encephalopathy with Severity of Neurological Damage

Thesis

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Sara Fekry Fouad

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Abbreviations

aEEG .....Amplitude-integrated electroencephalography.

AG3340 ..... (prinomastat) a small molecule hydroxamate-based Inhibitr of MMP-9

AMP/QA.... amino hydroxy methyl isoxazolepropionic acid

ATP..... adenosine triphosphate

BBB ..... blood brain barrier

BGT ..... basal ganglia and thalamus

BPD ..... bronchopulmonary dysplasia

CA1..... Tumormarker

CBF..... Cerebral blood flow

CBF..... Cerebral blood flow

CK..... Creatine Kinase

CLD ..... Chronic lung disease

CNS..... Central nervous system

CSF ..... Cerebrospinal fluid

ECM..... Extracellular matrix

EEG ..... Electroencephalography

EPO ..... Erythropoietin

FGF..... Fibroblast growth factor

FGFR1 ..... Fibroblast growth factor receptor 1.

FT..... Fullterm

GM6001 ..... The broad-spectrum MMP inhibitor

GMI..... Monosialogangliosides

GPI ..... Glycosylphosphatidylinositol

H-I ..... Hypoxia –ischemia

HIE ..... Hypoxic ischemic encephalopathy

HIF..... Hypoxia-inducing factor

HIV ..... Human immunodeficiency disease

HMD..... Hyaline membrane disease

HT ..... Hemorrhagic transformation

ICH ..... Intracranial hemorrhage

IGFBP-3 .... Insulin-like growth factor binding protein 3

IGFBPS .... Insulin growth factors binding proteins

IL1b ..... Interleukin 1 b

IPPV ..... Intermittent positive pressure ventilation

IUGR ..... Intauterine growth retardation

IVH ..... Interventricular heamorrhage

IVH ..... Intraventricular hemorrhage

LDH ..... Lactate dehydrogenase

MCAO ..... Middle cerebral artery ocllusion

MCP ..... Membrane Cofactor Protein

MCP-3 ..... Membrane Cofactor Protein-3

MMPs..... Matrix Metalloproteinases

MT-MMPs Membrane-Tight Matrix Matalloproteinase

NAA ..... N-acetylaspartate

NEC ..... Necrotizing enterocolitis

NMDA..... N-methyle-D-aspartate receptors

NOS ..... Nitric oxide synthase

PET..... Positron Emission Tomography

PLIC ..... Posterior limb of the internal capsule

PPROM..... Premature rupture of membrane

PT ..... Preterm

PTD ..... Preterm delivery

PV/IVH..... Periventricular-intraventricular hemorrhage

PVL ..... Periventricular leukomalacia

RI ..... Resistive index

ROP Retinopathy of prematurity

S&S..... Sarnat and sarnat staging

SB-3CT..... The gelatinase-selective compound.

SDF-1α..... Sodium dodecyle sulfate-one alfa.

SEP ..... Somatosensory evoked potential.

SIADH..... Syndrome of inaproprite antidiuretic hormone

SPECT..... Single photon emission computed tomography

SPTL..... Spontaneous preterm labor.

SVZ ..... Subventricular zone.

Tc99 ..... Technetium

TIMPs..... Tissue inhibitor of metalloproteinase.

TNF-α ..... Tumour necrosis factor alfa.

WM..... White matter

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Introduction

Hypoxia is generally defined as the partial or complete lack of oxygen in the brain or blood ***(Martin et al., 1983).*** Hypoxic injury in the fetal and neonatal brain results in neonatal mortality, morbidity or long term sequel such as cerebral palsy, mental retardation, epilepsy and learning disability. In term neonates, 1-4% of infants suffer birth asphyxia and one third manifest significant neurological deficits ***(Sharda, 2006).***

The incidence of moderate or severe Hypoxic Ischemic Encephalopathy (HIE) has remained essentially unchanged over the last 20 years, at 1.5 to 2 per 1000 live birth in United States. Approximately 15 to 20 percent of these infants will die, and 20 to 25 percent of those who survive will be disable ***(Dixon et al., 2002).***

Matrix Metalloproteinases (MMRs) compromise an important family of proteases associated with basement membrane and extracellular matrix remodeling and are involved in both physiological and pathological CNS processes ***(Pagenstecher et al., 1998.)***

Matrix Metalloproteinase-9 has been implicated specifically in cerebral ischemia ***(Lo et al., 2002).*** Recently, it has been suggested that MMPs may be upregulated in hippocampus after global brain ischemia ***(Rivera et al., 2002).*** Moreover, ***(Lee et al., 2004)*** reported that inhibition with a broad-spectrum metalloproteinase inhibitor ameliorates dysregulated gelatinase activity and reduces hippocampal neuronal death after transient global cerebal ischemia in mice.

Aim of the Work

This study is designed to evaluate the serum level of MMP-9 and its correlation with neurological damage among neonates with HIE.

Hypoxic Ischemic Encephalopathy

Background

Hypoxic-ischemic encephalopathy is a severe complication of asphyxia that occurs before, during, or after birth. It can result in death or neurological damage, which can manifest in the short term (within 12–24) hours as seizures, altered reflexes, or altered level of consciousness (or a combination), and in the longer term by developmental delay, epilepsy, mental retardation, or cerebral palsy (or a combination) ***(Carli et al., 2004).***

New infants who sustain an acute intrapartum hypoxic-ischemic insult of sufficient magnitude to result in long-term neurologic sequelae invariably have recognizable clinical encephalopathy during the first days of life. These infants have evidence of derangements in many organs. Their cerebral function is depressed at birth and remains depressed for days or weeks, and they frequently have seizures soon after birth ***(Vannucci and Hagberg, 2004).***

Depending on the extent and location of the insult, the infants can develop spastic paresis, choreoathetosis, ataxia and disorder of sensorimotor coordination later on. It is also common for these infants to develop later damage to the auditory and visual systems and impairment of intellectual ability. Despite the severe clinical and socioeconomic significance, no effective therapeutic strategies have yet been developed to count for this condition, one possible explanation being that perinatal management up to now has focused on preventing hypoxic-ischemic brain damage altogether ***(Volpe, 2001).***

EPIDEMIOLOGY AND INCIDENCE

Severe perinatal asphyxia with hypoxic-ischemic encephalopathy occurs for approximately 1 or 2 newborns per 1000 live births; of these 0.3 per 1000 demonstrate significant neurologic sequelae ***(Volpe, 2001).***

Hypoxic ischemic encephalopathy occurs in about 0.5 – 0.75 per 1000 deliveries and neurological handicaps are present in 25% to 28% of the affected infants ***(Gazzolo et al., 2004).***