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The Relationship between Procalcitonin and Delirium among Elderly

Thesis

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List of Abbreviations

ACh	Acetylcholine
ADL	Activities of daily living
APACHE II	Acute physiology and chronic health evaluation II score
APOE	Apolipoprotein E
BBB	Blood brain barrier
BDNF	Brain derived neurotrophic factor
BUN	Blood urea nitrogen
CAM	The confusion assessment method
CBC	Complete blood count
CLD	Chronic Liver Disease
CNS	Central Nervous System
COMT	Cetechol- Omethyl transferase
CRP	C reactive protein
CSDD	Cornell Scale for Depression in Dementia
CSF	Cerebrospinal fluid
DLB	Dementia with Lewy Bodies
DM	Diabetes Mellitus
DRD2	Dopamine recptor 2 gene
DSM IV TR	Diagnostic and statistical manual of mental disorders, Fourth edition, Text Revision
ESR	Erythrocytes sedmintation rate
FDA	Food and Drug Administration
FUO	Fever of unknown origin
GABA	Gamma amino butyric acid
GDS	Geriatric depression scale

HELP	Hospital elder life program
HTN	Hypertension
IADL	Instrumental Activities of daily living
ICD	International Classification of Diseases
ICU	Intensive care unit
IHD	Ischemic Heart Disease
LNAA	Large neutral amino acid
LPS	Lipopolysaccharide
MMSE	Mini mental Status Examination
NES	Neuron specific enolase
PCT	Procalcitonin
PJI	Prosthetic joint infection
POCD	Post operative cognitive dysfunction
POD	Post operative delirium
RA	Rheumatoid arthritis
S100 β	S100 calcium binding protein
SAA	Serum anticholinergic activity
SLC6A3	Solute carrier family 6,member 3
SLE	*Systemic lupus erythematosus*
SSD	Subsyndroml delirium
TNF	Tumor necrosis factor
TRP	Tryptophan
WBCS	White blood cells

Introduction

Delirium is a common clinical syndrome in elderly characterized by inattention and acute cognitive dysfunction. Delirium affects 14% - 56% of the elderly hospitalized patients **(Fong et al., 2009).**

Most literature about delirium emphasizes the problem of poor identification of delirium by hospital physicians. Hypoactive rather than hyperactive delirium is particularly missed because of the seemingly non-alarming symptoms **(Lyons, 2006).**

Delirium is associated with loss of independence, morbidity, mortality, and increased health care costs **(Inouye, 2006)**.

In the long term, delirium is associated with a more than 12-fold increased risk for developing dementia resulting in permanent impairment of cognitive function that is associated with altered levels of amyloid-b. The association between biomarkers in delirious patients and long-term cognitive function is unknown (**Witlox et al., 2010)**.

Despite these serious effects on outcome, the pathogenesis of delirium is still incompletely understood is unknown **(Maclullich et al., 2008)**.

Delirium is thought to be the result of alterations in neurotransmission, inflammation, and/or cerebral blood flow ***(*Gunther et al., 2008)**.

These alterations could be associated with cell death in the central nervous system (CNS), but there is no direct evidence of neuron/glial cell death in delirious Patients (**Lewin et al., 1996)**.

Because the pathogenesis of delirium is probable multifactorial, biomarker analysis may provide valuable information regarding the underlying mechanism **(Maclullich et al., 2008).**

Several biomarkers have been associated with delirium **(Flacker et al., 1998).**

Procalcitonin (PCT) play a role in inflammation directly associated with delirium **(Lesur et al., 2010).**

PCT is a 116 amino acid precursor of calcitonin which under normal circumstances is produced by the thyroid C-cells**,** in circumstances of systemic inflammation PCT is produced in large quantities by many body tissues; PCT levels parallel the severity of the inflammatory insult or infection. Furthermore, PCT has some utility as a prognostic indicator with higher serum concentrations related to the risk of mortality **(Kibes et al., 2011).**

In a cohort of sepsis patients admitted to the Intensive care unit(ICU), it has been found that higher baseline levels of PCT or C-reactive protein(CRP) were associated with more days of delirium **(Mcgrane et al., 2011).**

Aim of the Work

To assess relationship between PCT and delirium among a sample of Egyptian elderly patients.

Delirium in elderly

Delirium is an acute neuropsychiatric disorder characterized by impaired attention, disturbed consciousness and disorganized thinking **(Brown *et al.*, 2011).**

It is a non specific but reversible manifestation of acute illness. It is commonly associated with surgery, infection or critical illness **(Inouye et al., 2014).**

Based on Diagnostic and Statistical Manual of Mental Disorders Fourth edition, Text Revision (DSM-IV-TR) criteria, delirium is characterized by the rapid onset of symptoms (usually hours or days) and tends to fluctuate, with an altered level of consciousness, with an inability to focus, sustain or shift attention and a change in cognition (such as memory impairment, disorientation, language disturbance) or development of a perceptual disturbance that is not better accounted for by dementia. Moreover, there is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition, or substance intoxication/withdrawal or due to multiple etiologies **(APA, 2000).**

The word delirium is derived from the Latin term *delirare*, meaning to become "crazy or to rave". It has been documented in medical literature for more than 2000 years with affair consistent clinical description **(Adamis et al., 2007).**

It was reported during the time of Hippocrates, who used the words *phrenitis* (frenzy) and *lethargus* (lethargy) to describe the hyperactive and hypoactive subtypes of delirium. As a medical term delirium was first used by Celsus in the first century to describe mental disorders associated with

fever or head trauma **(Khan et al., 2009).**

A variety of terms have been used in the literature to describe delirium, including acute confusional state, acute brain syndrome, acute cerebral insufficiency, and toxic-metabolic encephalopathy **(Morandi et al., 2008).** But delirium is now the preferred term **(Gill and Mayou, 2000)** and it has been suggested that acute confusional state should be the only accepted synonym for this syndrome **(Lipowski, 1992).**

Epidemiology:

Delirium is a common and serious condition among the elderly, particularly in hospitalized patients. It affect up to 30% of this patient population **(Saxena and Lawley, 2009)**. Delirium is reported in 40% to 60% of non-ventilated and 60% to 89% of mechanically ventilated patients in the ICU **(Inouye, 2014).**

Higher rates are also reported in surgical settings with an incidence reported to range from 10 to 70% after surgery **(Guenther and Radtke, 2011)**. Especially in patients undergoing cardiothoracic surgery, emergency orthopedic procedures, vascular surgery or cataract removal **(Saxena and Lawley, 2009).**

In a recent study **(McCusker et al., 2011**) the prevalence of delirium has been estimated between 3.4 and 33.3%. In the community as expected, the prevalence is lower ranging from 1 to 2% (**Popeo, 2011).**

Etiology:

The etiology of delirium is usually multifactorial, resulting commonly from a combination of predisposing and precipitating factors. The pathophysiological mechanisms remain poorly understood. While some evidence for the contribution of neurotransmission disruption, inflammation,

or acute stress responses **(Saxena and Lawley, 2009).**

The most common predisposing factors are: advanced age, male gender, pre-existing dementia and depression, visual and hearing impairment, functional dependence, dehydration, malnutrition, poly medication (mainly psychoactive drugs), alcohol abuse and coexistence of multiple and severe medical conditions **(Saxena and Lawley, 2009).**

The most common precipitating factors are: inter current illnesses (e.g., infections), iatrogenic complications, metabolic derangements, primary neurological conditions, surgery, drugs (particularly benzodiazepines, narcotic analgesics, and drugs with anti-cholinergic effects. Uncontrolled pain has also been associated with the development of delirium, Environmental factors, such as admission to an ICU, use of physical restraints or bladder catheterization have also been implicated **(Saxena and Lawley, 2009).**

Pathophysiology:

At present, the pathophysiology of delirium is not fully understood **(Reade et al., 2014)**. However, current evidence suggests that disruption of neurotransmission can contribute to the development of this disorder **(Saxena and Lawley, 2009).**

There are a number of neurotransmitters believed to be involved in the pathogenesis of delirium, including acetylcholine, serotonin, dopamine and gamma amino butyric acid (GABA) **(Gunther et al., 2008).**

The cholinergic system has an important role in cognition and attention and it has impact in the development of delirium **(Hshieh et al., 2008).** In Alzheimer's disease, there is loss of cholinergic activity which may contribute to cognitive decline and carry an increased risk of delirium. The risk of delirium is higher in patients using concomitant anticholinergic

medications **(Hshieh.et al., 2008).**

Other neurotransmitter abnormalities that are associated with delirium include elevated brain dopaminergic function and a relative imbalance between the dopaminergic and cholinergic systems **(Trzepacz, 2000**).

Serotonin is a major excitatory neurotransmitter in the brain, and its production depends on the precursor tryptophan (TRP). It is postulated that a decrease in TRP levels may lead to a decrease in serotonin which may lead to the development of delirium **(Gunther et al., 2008)**.

Inflammation or acute stress responses are less supported Pathophysiological mechanisms **(Fong et al., 2009).** The first has been inferred from basic and clinical research literature evidence, supporting the hypothesis that trauma and infection or surgery can lead to increased production of cytokines **(Cerejeira et al., 2010).** This mechanism may induce delirium in susceptible patients **(Maclullich et al., 2008).** A recent review concluded that this increase in cytokines plays important role specifically in the development of cognitive dysfunction observed in delirium **(Simone and Tan, 2011).**

In a prospective study by McGrane et al, inflammatory biomarkers PCT and CRP were measured in mechanically ventilated patients. Investigators found that higher levels of PCT and CRP were associated with delirium and less coma-free days, implicating inflammation as an important inflammatory changes within the brain **(McGrane et al., 2011).**

Advanced neuroimaging techniques might provide further insights into pathophysiology. Local and distant factors together account for overall and regional perfusion abnormalities noted in brains of people with delirium **(Pfister et al., 2008**). Total cerebral and regional perfusion are decreased as a result of impaired cardiac output **(Siepe et al., 2011**) and loss of cerebral