EXPLORATION AND APPLICATION OF BIOCHEMICAL MARKERS TO AID DIAGNOSIS OF CENTRAL NERVOUS SYSTEM INFECTIONS

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诊断中枢神经系统感染的生化指标的探索与应用

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STATEMENT OF ORIGINALITY

I hereby certify that the work embodied in the thesis is my own work, conducted under normal supervision. The thesis contains no material which has been accepted, or is being examined, for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968 and any approved embargo.

…….

Michael Zhang

To my wife, Pui Ling (Iris) Li, and my parents, Lian De Zhang and Zhu Jiao Yang,
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ABBREVIATIONS, PREFIXES AND SYMBOLS

ADL	Activity of daily living
ALT	Alanine transaminase
AM	Aseptic meningitis
AST	Aspartate transaminase
BBB	Blood brain barrier
BCB	Blood CSF barrier
BM	Bacterial meningitis
BOND	Biomarker of Neuro-infectious Disease
CIAP	CSF IgG / CSF Albumin Percentage
CIR	CNS Infection Risk
CNS	Central nervous system
CNSI	Central Nervous System Infections
CRP	C reactive protein
CSF	cerebrospinal fluid
CT	Computed tomography
CV	Coefficient of Variations
DOR	Diagnostic Odds Ratio
ED	Emergency department
ELISA	Enzyme Linked Immunosorbent assay
ESR	Erythrocyte sedimentation rate

FBC	Full blood count
FM	Fungal meningitis
GCS	Glasgow Coma Scale
GFAP	Glial fibrillary acidic protein
GFR	Glomerular filtration rate
GOSE	Glasgow outcome scale-extended
GP	General Practitioner
HDL	Highest Detectable Limit
ICP	Intracranial Pressure
ICU	Intensive care unit
IQR	Inter-Quartile Range
LDL	Lowest Detectable Limit
LOD	Level of Detection
LP	Lumbar puncture
LR+	Positive Likelihood Ratio
LR-	Negative Likelihood Ratio
MEL	Meningo-encephalitis
MMP	Matrix metalloproteinase
MS	Multiple sclerosis
NICU	Neonatal intensive care unit
NOS	Not Otherwise Specified
NSE	Neuronal specific enolase
OLS	Ordinary Least Square

OR	Odds Ratio
PCR	Polymerase chain reaction
PCT	Procalcitonin
PMN	Polymorphonuclear Cells (aka. Neutrophils)
Qalb	Albumin quotient
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RBC	Red blood cell
rDOR	Relative Diagnostic Odds Ratio
ROC	Receiver operating characteristics
ROD	Range of Detection
RRR	Relative Risk Ratio
SAH	Subarachnoid haemorrhage
SD	Standard deviation
SE	Standard error
TBI	Traumatic brain injury
TNF-α	Tumour Necrosis Factor - alpha
WBC	White blood cell
WCC	White Cell Count

ABSTRACT

Introduction

This thesis examines the diagnostic performance of a variety of clinical, serum and CSF markers to predict CNS infections. Many general inflammatory markers have been studied fairly extensively with relation to CNS infections, but the literature on the neural specific markers in CNS infections is still limited and the results are currently far from being conclusive. This thesis aims to explore a variety of inflammatory markers to enhance our understanding of their diagnostic accuracy for CNS infections, and then apply these markers to a cohort of patients to directly compare their diagnostic performance.

Methods

This thesis starts by launching a clinicians' survey to evaluate the contemporary clinical practice patterns for managing possible CNS infections.

This thesis then explores the diagnostic accuracy of a variety of clinical features, and general and neural specific markers, in the serum and in the CSF that have been published in the literature. This was accomplished by undertaking a systematic review and meta-analysis of these markers to compare their diagnostic performance for CNS infections.

This thesis finally undertook a prospective study to apply multiple general and neural specific markers in the serum and in the CSF on a cohort of patients who were suspected to have CNS infections.

Results

The clinician survey demonstrates the diagnostic dilemma and the issues of local clinicians managing patients with suspected CNS infections. The survey results also demonstrate the extent of evidence based medicine that influences these clinicians.

The systematic review and meta-analysis of multiple makers for all types of CNS infections shows a higher diagnostic accuracy of CSF markers overall in comparison with clinical features and the serum markers. Serum PCT and serum CRP were found to be excellent general inflammatory markers to distinguish certain types of CNS infections. From this literature

review, the literature on the neural specific markers that are used to predict CNS infections are still limited and inconclusive.

The prospective cohort study provided further evidence on some of the neural specific markers that were used to investigate patients with possible CNS infections. The higher levels of NSE and S100B in the CSF were reflective of the pathophysiological changes in the event of CNS infection. The results of this study also suggest the impairment of the blood brain barrier in CNS infections, especially in serious infection such as bacterial meningitis and meningoencephalitis. Higher serum S100B and NSE levels in these diagnostic sub-groups is believed to be caused by efflux of S100B and NSE from the intra-thecal space of CNS to systemic circulation as a result of a leaky blood brain barrier in these conditions. Although similar changes of concentration were not evident in this study for GFAP, the serum GFAP levels were very high in deceased patients and in patients with elevated intracranial pressure. Nevertheless, the results of this study did not indicate a superior diagnostic performance for CNS infections of these neural specific markers over other markers.

Conclusions

The results from this thesis highlight the challenging problem of predicting CNS infections by using individual markers. Whilst some of the neural specific biomarkers were observed to have higher levels in some patients with CNS infections than in the controls, the results of this and previous studies indicate that, given our best available evidence, the neural specific biomarkers being studied in this project, including S100B, NSE, and GFAP, do not appear to have a greater diagnostic accuracy for CNS infections than the other markers. However, a risk stratification model developed by combining S100B and meningism signs can be a helpful screening tool for the patients suspected to have CNS infections.