Medical Studies Department for Children

Early detection of Cognitive and Behavioral Sequelae in Children Survivors of Bacterial Meningitis

Thesis Submitted for partial Fulfillment of Master Degree in Medical Childhood Studies

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{قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا

إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ

الْعَلِيمُ الْحَكِيمُ}

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List of Abbreviations

ABM	Acute bacterial meningitis
ARDS	Adult respiratory distress syndrome
BM	bacterial meningitis
CDC	Centers for Disease Control and Prevention
CNS	CENTRAL NERVOUS SYSTEM
CSF	cerebrospinal fluid
CT	computed tomography
EF	executive functions
fMRI	functional magnetic resonance imaging
Hib	Haemophilus influenzae type b
IQ	intelligence quotient
MIC	minimum inhibitory concentration
MRI	magnetic resonance imaging
PFC	prefrontal cortex
PPSV	Pneumococcal polysaccharide vaccine
SD	Stander deviation
SIADH	Syndrome of Inappropriate Antidiuretic Hormone Secretion
WBCs	White blood cells
WHO	World Health Organization
WM	working memory

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INTRODUCTION AND AIM OF THE WORK

Introduction

Meningitis is inflammation of the protective membranes covering the brain and spinal cord, known collectively as the meninges ***(*Saez-Llorens and McCracken, 2003*).***

Meningitis is a serious public health problem demanding early diagnosis, effective treatment, prevention and control. It is a major cause of morbidity and mortality among infants and children ***(*Commey et al., 1994*).*** In Egypt, case-fatality rate ranged from 8.5 to 55% **(Youssef et al., 2004).**

The most recent epidemic, affecting Nigeria, Niger, Mali and Burkina Faso, started in January 2009 and is ongoing ***(*WHO, 2009*).***

Apart from endemicity, a violent epidemic disease occurs every 6 – 12 years in the African meningitis belt ***(*Tikhomirov et al., 1997*).*** Meningitis is considered as an endemic disease in Egypt ***(*Farag et al., 2005*).***

There are three main organisms that account for over 90% of the world's cases of meningitis in children which are Neisseria meningitidis, Streptococcus pneumonia and Haemophilus influenza type b ***(*Nabi et al., 1992).***

Complications of meningitis can be divided into systemic and neurologic. About 15% of surviving children develop sensorineural hearing loss, motor problems, seizures, or mental retardation after bacterial meningitis **(Kaplan et al., 2006).**

Cognitive deficiencies after bacterial meningitis in children (predominantly persistent difficulties in learning, deficits in short term memory, behavioral

problems and poor academic performance) have been described ***(*Grimwood et al., 2000*).***

Short term memory is the domain which is affected most frequently and most severely after bacterial meningitis ***(*Schmidt et al., 2006).***

Survivors of childhood bacterial meningitis may have increased behavioral problems over time (e.g. Somatic complaints, mood problems, social problems, thought problems, attention problems, and delinquent behavior) ***(*Halket et al., 2003*).***

Several studies have evaluated the intelligence quotient (IQ) of survivors of bacterial meningitis compared to their siblings or other control children ***(*Taylor et al., 1990*).*** Although not all of the studies found a difference in the mean IQ compared to controls (usually siblings), a greater proportion of children who had meningitis had IQ less than 70 ***(*Feigin and Cutrer, 2009*).***

More subtle adverse outcomes, such as cognitive academic and behavioral problems are present in 20% of bacterial meningitis survivals. But these more subtle problems often remain undetected until the child starts school which may be several years after he / she has been cured of meningitis ***(*Koomen et al., 2004*).***

Aim of the study

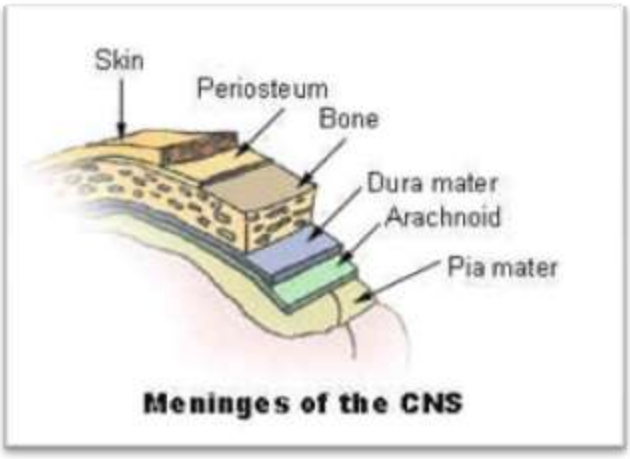
-Assess early cognitive and behavioral sequelae in children survived of bacterial meningitis.

-Detection of subtle deficits with relevant contribution to rehabilitation strategies, either by identifying deficits that can be addressed or capacities that can be used to facilitate functional recovery.

Anatomy of central nervous system

The central nervous system is made up of the brain and spinal cord. The major divisions of the human brain are the brainstem, cerebellum, diencephalon, and cerebral hemispheres. The meninges cover and protect the brain and spinal cord. There are three layers of meninges around the brain and spinal cord, Figure1. The outer layer, the dura mater, is a tough white fibrous connective tissue. The middle layer of meninges is the arachnoid which resembles a cobweb in appearance and is a thin layer with numerous threadlike strands that attach it to the innermost layer ***(Staner and Thomas, 2006)***.

The space under the arachnoid, the subarachnoid space, is filled with cerebrospinal fluid and contains blood vessels. The pia mater is the innermost layer of meninges. This thin, delicate membrane is tightly bound to the surface of the brain and spinal cord and cannot be dissected away without damaging the surface ***(Staner and Thomas, 2006)*.**



(Staner and Thomas, 2006)

Figure (1): Skin and the three layers of meninges**.**

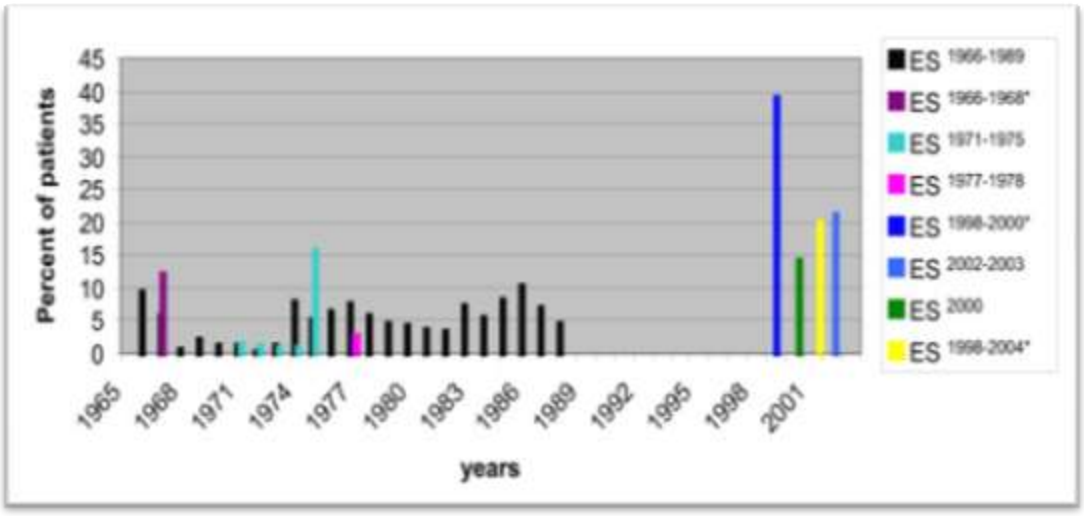
Epidemiology

Bacterial meningitis is accounting for an estimated 171000 deaths worldwide per year ***(*Luis Jodar et al., 2002*).*** Similarly bacterial meningitis occurs in about 3 people per 100,000 annually in western countries **(Attia et al., 1999).** The most recent epidemic, affecting Nigeria, Niger, Mali and Burkina Faso, started in January 2009 and is ongoing ***(WHO, 2009).*** Apart from endemicity, a violent epidemic disease occurs every 6 – 12 years in the African meningitis belt ***(Tikhomirov et al., 1997).*** Meningitis is considered as an endemic disease in Egypt ***(Farag et al., 2005).***

Almost all microbes that are pathogenic to human beings have the potential to cause meningitis, but a relatively small number of pathogens (i.e., group B streptococcus, Escherichia coli, Listeria monocytogenes, Haemophilus influenzae type b [Hib], Streptococcus pneumonia, and Neisseria meningitidis) account for most cases of acute bacterial meningitis in neonates and children ***(Kwang, 2010).*** There are three main organisms that account for over 90% of the world's cases of meningitis. These are Neisseria meningitidis, Streptococcus pneumonia and Haemophilus influenzae type b ***(Farag et al., 2005).***

Streptococcus pneumonia is a leading causative agent of diverse infections. In Egypt, it was recently described as the leading cause of bacterial meningitis skewing the epidemiology from Neisseria meningitidis, which was previously reported as the major etiological agent. Serotype distribution of Streptococcus pneumonia among meningitis patients are {6B, 1, 19A, 23F, 6A} which are

inadequately represented in the current 7- and 11-valent vaccine ***(Lamyaa and Rania, 2009)***.

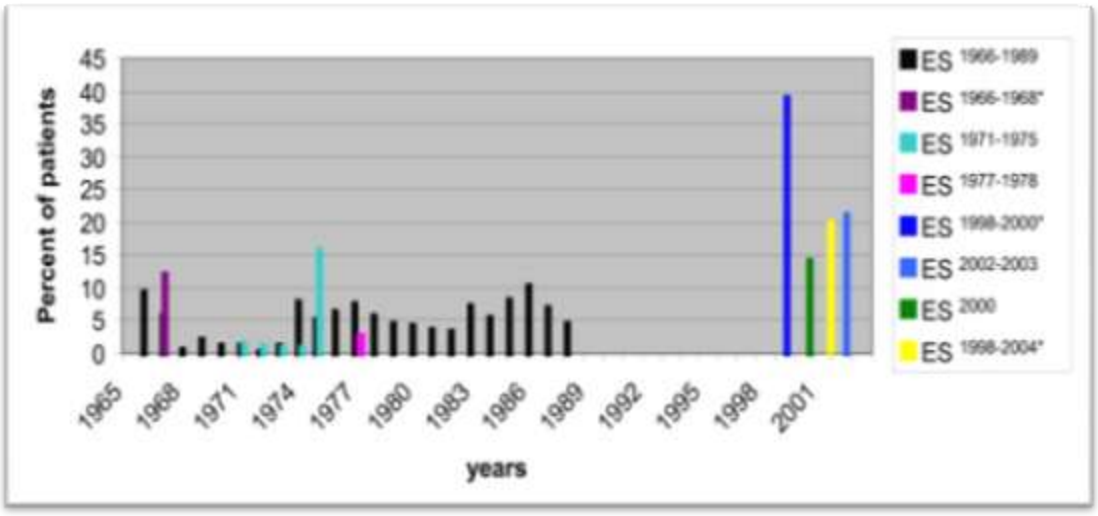


(Lamyaa and Rania, 2009)

Figure2. Percentage of pneumococcal meningitis cases based on studies conducted over 39 years.

Additionally, penicillin resistance in Streptococcus pneumonia induced meningitis was reported by several studies at different time intervals, with an increase in the pattern of resistance over time. In 1993 ,71% of Streptococcus pneumonia isolates were susceptible to penicillin ***(Ostroff et al., 1996)***; in 2000 , 63% of isolates were susceptible to penicillin ***(El Kholy et al., 2003)*** and in 2004, 51% of isolates were susceptible to penicillin. Also high rates of resistance to penicillin were detected in 1298 Streptococcus pneumonia positive blood and spinal fluid cultures collected from meningitis patients over a 36-month period ***(Borg et al., 2009)***. On the other hand, susceptibility to chloramphenicol and ceftriaxone was 79% and 100%, respectively ***(Youssef et al., 2004)*.**

Therefore periodic monitoring of the patterns of antimicrobial resistance is necessary to guide effective treatment ***(Afifi et al., 2007).***



(Lamyaa and Rania ,2009)

Figure 3: Percentage of Meningitis Cases Caused by ***Haemophilus influenzae*** cases based on studies conducted over 39 years**.**

In a laboratory-based surveillance (1998-2004) carried out to identify the etiological agent of bacterial meningitis, *Haemophilus influenza* was found to be the second leading cause following Streptococcus pneumonia responsible for 20% of the 843 cases of culture positive patients. Among children less than 5 year *Haemophilus influenzae* was the most common bacteria isolated. The mean age was 7 months ***(Lamyaa and Rania, 2009)*** Figure 3.

In Egypt, the majority of *Haemophilus influenzae* strains tested were resistant to ampicillin or chloramphenicol suggesting the need for routine use of ceftriaxone as first line therapy ***(Youssef et al., 2004).***