The Etiology

Of Bacterial Meningitis

In Children Aged 2-60 Months Diagnosed

At Queen Elizabeth Hospital, Kota Kinabalu: Before And After the

Introduction of Hemophilus influenzae (Hib) Vaccine

By

Dr. ASMIATI ABD HAMID

Dissertation Submitted

In Partial Fulfillment of The Requirements

For The Degree Master of Medicine

(Pediatrics)

2007

ACKNOWLEDGEMENT

I would like to thank the Head of Pediatric Department, HUSM, Dr Noorizan Abd Majid for all her support and courage. Also to Head of Pediatric Department, Likas Hospital, Kota Kinabalu, Sabah (formerly known as Pediatric Department, Queen Elizabeth Hospital), Dr Soo Thian Lian for his support and understanding. Not to forget, to my supervisor, Dr. Mohd Suhaimi Ab. Wahab for all his time and courage. Lastly, I would like to thank En Dominic, Record Office, Queen Elizabeth Hospital, Kota Kinabalu for his help and kindness. Without any of them, this study will be very difficult to pursue.

Table of Contents

List of Tables

List of Figures

List of Symbols, Abbreviations or Nomenclature

BM	Bacterial meningitis
CSF	Cerebrospinal fluid
QEH	Queen Elizabeth Hospital
Hib	*Hemophilus influenzae* type b
GBS	Group B streptococcus
WBCs	White blood cells
WHO	World Health Organization

ABSTRAK

Latar belakang:

Meningitis di kalangan kanak-kanak boleh mengakibatkan kecacatan kekal dan kematian. Bakteria hemophilus influenzae jenis b (Hib) adalah penyebab utama bagi meningitis di kalangan kanak-kanak yang berumur 5 tahun ke bawah. Beberapa kajian di seluruh dunia telah membuktikan bahawa vaksin Hib amat berkesan untuk mengelakkan jangkitan kuman ini. Semenjak vaksin Hib disenaraikan di dalam jadual Immunisasi Kanak-kanak di Malaysia pada bulan Jun 2002, belum ada kajian dilakukan di negara ini tentang keberkesanan vaksin tersebut dalam mengelakkan jangkitan kuman Hib.

Objektif:

Objektif kajian ini adalah untuk memperolehi data berkenaan kekerapan jangkitan meningitis yang disebabkan oleh kuman Hib di kalangan kanak-kanak yang berusia 2 hingga 60 bulan di Hospital Queen Elizabeth, Kota Kinabalu, sebelum dan selepas vaksin Hib diperkenalkan. Kajian ini juga bertujuan untuk mengenal pasti kekerapan jangkitan kuman-kuman lain yang menyebabkan meningitis.

Tatacara:

Ini adalah kajian retrospektif yang dijalankan di Hospital Queen Elizabeth, Kota Kinabalu. Semua fail pesakit meningitis akan di kenal pasti melalui rekod hospital dan pesakit mestilah berusia 2 hingga 60 bulan semasa diagnosa di buat. Pesakit dibahagi kepada dua kumpulan, kumpulan pertama adalah pesakit yang di diagnosa pada Januari 1999 hingga Desember 2001 sebelum vaksin Hib diperkenalkan. Kumpulan kedua adalah pesakit yang di diagnosa pada Januari 2004 hingga Desember 2006 iaitu selepas vaksin Hib diperkenalkan. Semua data berkenaan pesakit dan keputusan pemeriksaan cecair serebrospinal akan direkodkan. Kuman penyebab meningitis akan di kenal pasti melalui kultur atau ujian latex. Data klinikal akan dianalisis menggunakan SPSS versi 12.0 dan STATA.

Keputusan:

216 pesakit dikenalpasti. 103 pesakit sebelum vaksin Hib diperkenalkan dan 113 pesakit selepas vaksin Hib diperkenalkan. Keputusan menunjukkan meningitis yang disebabkan oleh jangkitan kuman Hib telah berkurangan semenjak vaksin Hib diperkenalkan daripada 33% ke 6.2% (p:<0.001). Secara keseluruhannya, kekerapan Hib meningitis bagi seluruh populasi berkurang dari 2.27 ke 0.3 kes bagi setiap 100,000 penduduk, dan berkurang dari 21 ke 2.85 kes bagi 100,000 kanak-kanak berusia kurang dari 5 tahun. Komplikasi daripada jangkitan Hib ini juga telah berkurangan dan tiada mortaliti. Bagaimanapun, meningitis yang disebabkan oleh jangkitan kuman *Streptococcus pneumonia* adalah semakin meningkat semenjak vaksin Hib diperkenalkan daripada 5.8% ke 18.6% (p:0.003)

Kesimpulan:

Kewujudan vaksin Hib bukan saja telah mengurangkan kekerapan jangkitan Hib meningitis tetapi mengurangkan kes meningitis secara keseluruhannya. Komplikasi akibat meningitis juga semakin berkurangan dan tiada mortaliti. Bagaimanapun, meningitis yang disebabkan oleh kuman *Sterptococcus pneumonia* adalah lebih kerap berlaku di sepanjang tempoh kajian ini dijalankan.

ABSTRACT

Summary:

Bacterial meningitis in children is a serious threat to global health. Hemophilus influenzae type b (Hib) was an important cause of bacterial meningitis in children less than 5 years old prior to the introduction of Hib conjugate vaccine. Several studies have proven the effectiveness of routine Hib vaccination in protecting Hib meningitis worldwide. Since the implementation of Hib conjugate vaccine in Malaysian Primary Immunization Program in June 2002, no study has been done to evaluate the effectiveness of this vaccination against Hib meningitis in this country.

Objectives:

The objective of this study is to establish a local data about the incidence of Hib meningitis and the effectiveness of Hib vaccination against the disease among children aged 2 to 60 months in Queen Elizabeth Hospital, Kota Kinabalu, Sabah, Malaysia. We also look at the pattern of etiological agents of bacterial meningitis following a routine use of Hib vaccine.

Method:

This was a retrospective study, conducted at Queen Elizabeth Hospital, Kota Kinabalu, Sabah, Malaysia. All case notes of patients with meningitis admitted before Hib conjugate vaccine introduced from Jan 1999 to Dec 2001 and after the implementation of the vaccine between Jan 2004 to Dec 2006 were evaluated in the study. The patient must be aged between 2 to 60 months at the time of the diagnosis and the diagnosis was confirmed by clinical findings and cerebrospinal fluid assessment (CSF). The etiologic agents were based on positive CSF culture and/or latex agglutination test. Clinical information from the case notes, including CSF results and the outcome on discharge, were obtained. Analysis of extracted data was performed using SPSS version 12.0 and STATA.

Results:

216 case notes of patients were included in the study, 103 patients before and 113 patients after the introduction of the Hib vaccine. Hib meningitis incidence decreased from 2.27 to 0.3 cases per 100 000 overall population, and from 21 to 2.85 cases per 100 000 population in children less than 5 year. Hib meningitis before the vaccination was 33.0% (95% CI 24.0, 43.0) and after the introduction of the Hib vaccine Hib meningitis significantly reduced to 6.2% (95% CI 2,5, 12.4) (p:<0.001). Following the Hib vaccination, the complications were less severe and the mortality from Hib meningitis was significantly reduced. Pneumococcal meningitis however, was notably increased in

frequency from 5.8% before the Hib vaccine period to 18.6% after the implementation of Hib vaccine. Other organisms that caused bacterial meningitis were not affected by the Hib vaccination.

Conclusion:

The implementation of the Hib vaccine not only reduced the incidence of Hib meningitis but has reduced the incidence of bacterial meningitis as a whole. Patients with Hib meningitis who received Hib vaccination has developed less severe complications and results in less mortality. Pneumococcal meningitis however, alarmingly increased during the period studied.

CHAPTER 1 : INTRODUCTION

1.1 BACKGROUD

Meningitis is the inflammation of the two meningeal membranes, arachnoid and piamater that surround the brain and the spinal cord. Microbiologic causes of meningitis include bacteria, viruses, fungi, and parasites. Bacterial meningitis (BM) is among the most common causes of meningitis worldwide. In the process of meningitis, inflammatory cells spill into the cerebrospinal fluid (CSF) from the meninges, producing an increased cell count and biochemical changes.

In the past few years, significant advances have been made in understanding the pathophysiology of bacterial meningitis and in developing approaches to management. Despite these developments, bacterial meningitis remains an important cause of childhood mortality and those who survive are at high risk of developing neurological disability. Therefore, prompt and accurate diagnosis and adequate treatment of bacterial meningitis in children is still a major challenge.

Before 1990, *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Hemophilus influenzae* type b (Hib) are most commonly associated with bacterial meningitis, globally accounting for almost 90% of the reported cases of acute bacterial meningitis in infants over 60 days of age and also in young children [1]. In prospective population-based surveillance for bacterial meningitis in the United States in 1986, Hib was found to be the single most common

pathogen, responsible for 45% of cases, with an incidence of 2.9 cases per 100,000 populations. Most cases of Hib meningitis occurred in infants and children, with peak incidence in those less than 12 months of age [2].

Introduction of Hib polysaccharide-protein conjugate vaccines have dramatically reduced the burden of Hib invasive disease in the last 20 years [2,4]. Clinical trials demonstrated that conjugate vaccines have an efficacy of 90-100% in preventing Hib invasive disease in countries where the vaccine has been used extensively [5,10]. Since the introduction of the conjugate vaccine in the United States in 1988, the incidence of invasive Hib in infants and children under 5 years of age has declined from 421 cases per 100,000 population in 1987 to less than 0.7 per 100,000 population in 1997 [3,6]. Furthermore, the vaccine has been highly effective, even in the populations where coverage is not complete , due to its ability to reduce nasopharyngeal colonization in immunized individuals and also due to the effect of herd immunity [7,11.12].

The priority for Hib invasive disease is to extend the benefits afforded by conjugate vaccines to the developing countries. Worldwide, in 2003, 61% of children in target age groups for immunization were not routinely vaccinated against Hib. This causes approximately 300,000-400,000 death annually [8,9]., The burden of Hib infection in Malaysia was once documented incidence of less than 16 per 100,000 populations [123,124]. This is lower than that reported incidence in industrialized countries. The possible reason to explain this low incidence is under reporting data as the actual incidence is likely to be higher in Malaysia [13]. Hib vaccine was introduced in Malaysian primary immunization schedule in June 2002

at 2, 3 and 5 months of life and has shown the effectiveness but the long term impact of these programs has not been evaluated in the region. In Sabah, located at East Malaysia, the vaccine uptake reaches more than 70% by January 2003 and about 95% by the year 2004 [14]. Being the only referral center in west coast of Sabah, the incidence of meningitis in children in Queen Elizabeth Hospital ranged from 60 to 80 cases per year with more than 65% proven organism from a CSF culture [15].

The success of this conjugate vaccine in eliminating the Hib invasive disease has been postulated to be responsible for the changes in the etiological pattern of bacterial meningitis worldwide.

1.2 ETIOLOGY OF MENINGITIS

A wide range of bacteria causes purulent meningitis. In the neonatal period, which include premature and term babies, group B streptococci (GBS) cause most bacterial meningitis in many developed countries [24]. Most cases are caused by subtype III strain, and the disease usually arises after the first week of life but sometimes can be as late as 3 months of age. Coliform bacilli are the second most common in this population, especially strains of *Escherichia coli* possessing K1 antigen. In many developing countries, *E coli* and other gram-negative bacilli such as species of *Klebsiella, Enterococci,* and *Salmonella*, are the leading cause of meningitis in newborns [25]. *Listeria monocytogenes* is occasionally responsible for bacterial meningitis in this age group, especially during zoonotic outbreaks

[26,27]. As with GBS infections, meningeal infection caused by *L monocytogenes* usually happens after the first week of life. *Listeria* serotype IVb has been implicated in most cases. In infant and small children, *Streptococcus pneumonia, Neisseria meningitides*, and *Hemophilus influenzae* type b (Hib) are the most common pathogens. Children older than 5 years and adults are most exclusively affected by *S pneumonia* and *N meningitides*. In immunocompromised hosts and in patient undergoing neurosurgical procedures, meningitis can be caused by various different bacteria such as *Staphylococcus* species, gram-negative enteric bacilli, or *Pseudominas aerugenosa* [28].

Although more than 90 serotypes of pneumococci have been identified on the basis of their capsular polysaccharides, few are commonly associated with invasive disease and with meningitis. Almost all penicillin-resistant pneumococcal strains causing meningitis belong to serotypes 6, 9, 14, 18, and 23 [31].

Meningococci have been divided into serogroups on the basis of antigenic differences in their capsular polysaccharide (A, B, C, D, X, Y, Z, W-135, and 29-E). Group B, C, Y, and W-135 are the predominant serogroups associated with invasive disease in the US and in other developed countries, whereas the groups A strain accounts for epidemic disease in many other countries, especially sub-Saharan Africa [32]. Group B strains are more commonly isolates in Latin America. Meningococcal serotypes are defined on the basis of antigenic differences in the class 2 and 3 outer membrane proteins, whereas differences in the class 1 outer membrane proteins determine subtypes. More than 20 serotypes and at least 10 class 1 subtypes have been identified [33].

1.2.1 *Hemophilus influnzae*

Hemophilus influenzae is a small, non-motile Gram-negative cocco-bacilli in the family *Pasteurellaceae*. There are 2 major groupings of *H. influenzae*: encapsulated and non-encapsulated. It commonly colonies the respiratory tract and is a respiratory pathogen. *H influenzae* is highly adapted to its human host. It is present in the nasopharyx of approximately 75% of healthy children and adults. It is rarely encountered in the oral cavity and it has not been detected in any other animal species. It is usually the non encapsulated strains that are harbored as normal flora, but a minority of healthy individuals (3-7%) intermittently harbors *H influenzae* type b (Hib). Encapsulated strains of *H influenzae* are responsible for invasive disease [49,100]. These encapsulated strains are classified by capsular polysaccharide type's a-f; however, more than 95% of invasive disease is caused by *H influenzae* type b (Hib) [48,100]. Pharyngeal carriage of Hib is important in the transmission of the bacterium. With the routine use of conjugated vaccines against the b type strain in many countries, disease caused by this organism has almost disappeared [2,6,29,30]. In the United State (US) and most industrialized countries, Hib invasive disease especially bacterial meningitis has been eventually eliminated [2,3,4].

1.3 EPIDEMIOLOFY OF MENINGITIS

The frequency of neonatal meningitis varies greatly between different institutions and geographical areas, with rates of about 2 – 10 cases per 10 000 live births [34,35]. More than two thirds of all cases of neonatal meningitis in developed countries are caused by GBS and

gram-negative enteric bacilli. *L monocytogenes* is encountered occasionally, and usually associated with maternal infection acquired from contaminated milk products. In developing countries, gram-negative enteric bacilli are the predominant organism causing bacterial meningitis in the newborns; however, GBS and *L monocytogenes* have been increasingly isolated.

Hib meningitis is mainly a disease of infancy. Babies in the first year of life have the highest rates; mostly within the age of 2 months to 3 years. The disease is uncommon in infants younger than 2 months or in children more than 5 years of age. During the first few months of life, most infants are protected by passively acquired maternal antibodies. Children naturally developed immunity to Hib after the third year of life, and the concentrations of polyribosylribitol phosphate antibodies will reaches adult value by 7 years of age.

Meningococcal and pnemococcal meningitis are at their highest rate after the first year of life and rarely occur in infants younger than 2 months of age. Unlike Hib infections, these two organisms can cause systemic infection at any age in both children and adults. Poor living conditions and the crowded attendance in day care facilities has increased the risk of meningitis. However, the increased of meningitis rate in some ethnic groups (American Indian and black people) and some families, and the observation that siblings of patients with meningitis can have deficient antibody synthesis against Hib, indicate that genetic predisposition to infection probably exists [35].

Most cases of meningitis arise sporadically; only meningococcal infections can occur in epidemic form. Almost similar to Hib, meningococci are transmitted from person to person by nasopharyngeal secretions from the patient or carrier, and transmission usually requires close contact. The risk of acquiring a secondary case of meningococcal or Hib disease is greatly increased after exposure to primary infection in the household [36,37].

1.4 PATHOPHYSIOLOGY OF MENINGITIS

Bacterial meningitis occurs when bacterial virulence factors overcome host defense mechanisms that normally protect against central nervous system infection in the subarachnoid space [16]. The initial step in the development is colonization of the nasopharynx by the organism. Many bacterial possess specialized surface structures, called fimbriae, which allow adherence to receptors on nasopharyngeal mucosal cells. Once colonization has occurred, the organism may locally invade tissues and gain access to the bloodstream. Common meningeal pathogen, such as pneumococci, meningococci, and Hib, possess an outer polysaccharide capsule that acts as a virulence factor by preventing phagocytosis as well as complement-pathway activation.

After survival and replication in the bloodstream, the organism may cross the blood-brain barrier and invade the subarachnoid space. When the pathogen have entered the central nervous system, they replicate rapidly and liberate active cells wall or membrane-associated components ie, lipoteichoic acid and peptidoglycan fragments of gram-positive organism, and lipopolysaccharide of gram-negative bacteria [17,18]. Host defense mechanisms are

unable to control infection in the cerebrospinal fluid (CSF) because of relatively low levels of local antibody and complement activity. Bacterial replication and accumulation of white blood cells (WBCs) in the CSF enhance a local inflammatory response in the subarachnoid space because of production and release of inflammatory mediators. Among these mediators are cytokines, interleukin-1, interleukin-6, tumor necrosis factor, prostaglandin E2, and leukotriene B4 [19,20].

Subsequently, leucocytes penetrate the intercellular junction of the capillary endothelium and release proteolytic products and toxic oxygen radicals. These events results in injury to the vascular endothelium and alteration of blood-brain barrier permeability. Dependant on the potency and duration of the inflammatory stimuli, the alterations in permeability allow penetration of serum proteins of low molecular-weight into the CSF, and lead to vasogenic edema. Additionally, large numbers of leukocytes enter the subarachnoid space and release toxic substances that contribute to the production of cytotoxic edema. As the results of the high protein and cell content, the increased viscosity of the CSF contributes to generation of interstitial edema [40,44].

All these inflammatory events, if they are not modulated promptly and effectively, eventually cause alteration of the CSF dynamics (brain edema, intracranial hypertension), brain metabolisms, and cerebrovascular auto regulation (reduced cerebral blood flow) [21,22,23]. These changes lead to life-threatening or long-term neurologic complications.

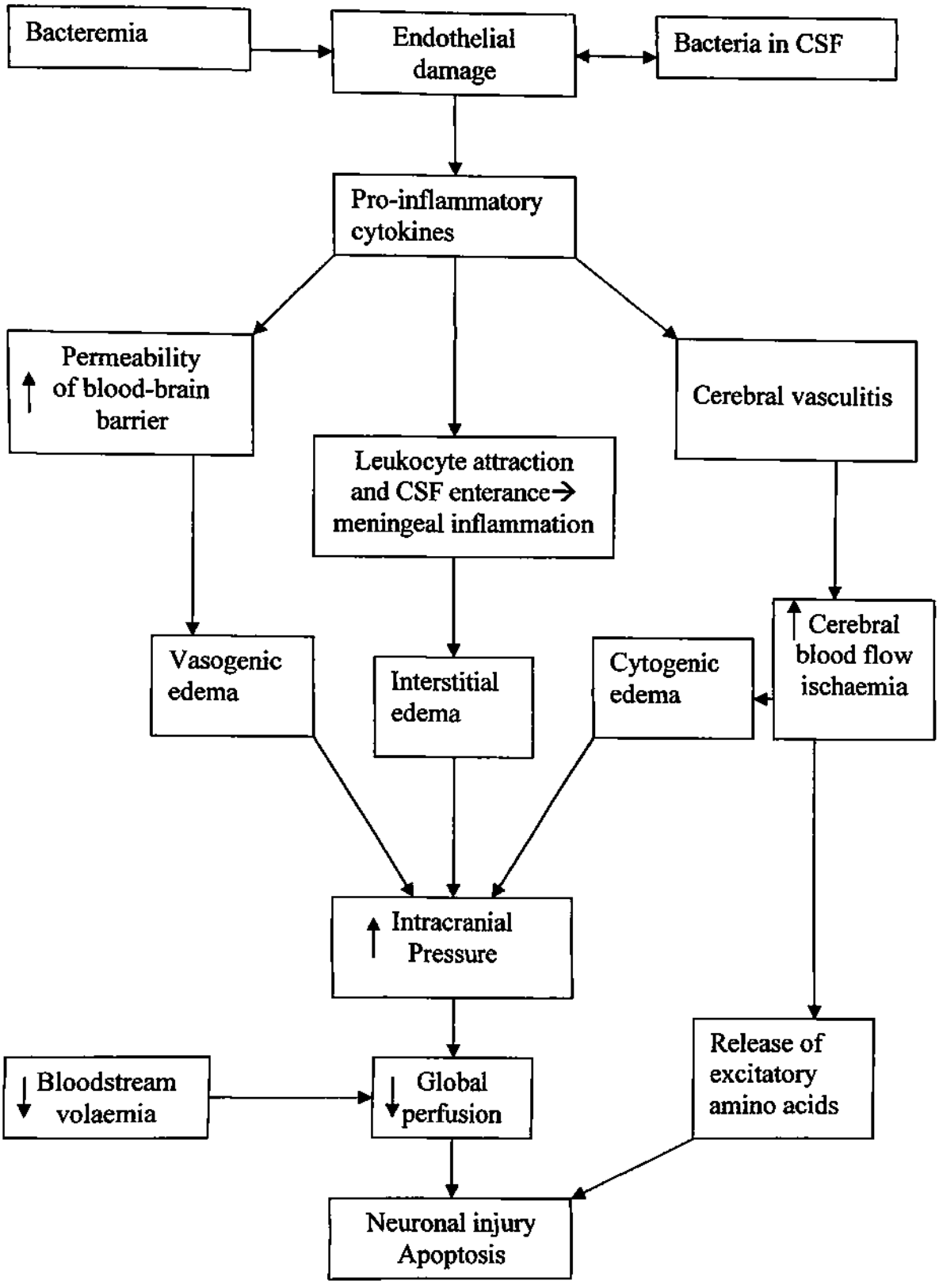

Figure 1.1 Pathophysiological cascade in bacterial meningitis adapted from Lancet 2003; 361: 2139-48; Seminar-Bacterial meningitis in children.